MEDICAL LIBRARY

FEB 23 1949

Volume X FEBRUARY 1949 Number 2

DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

CONTENTS:

ENTROPY, MENTAL DISEASE AND DEATH 35
Lewis Danziger, M.D., Wauwatosa, Wisconsin

PHENURONE IN EPILEPSY 47
Frederic A. Gibbs, M.D., Guy M. Everett, Ph.D. and R. K. Richards, M.D., Chicago, Illinois

THE USE OF SODIUM AMYTAL AND BENZEDRINE SULFATE IN THE SYMPTOMATIC TREATMENT OF DEPRESSIONS 50
Jacques S. Gottlieb, M.D., Iowa City, Iowa

THE DYNAMICS OF JUVENILE DELINQUENCY 53
Ludolf N. Bollmeier, M.D., Hot Springs, Arkansas

COMBINED PENICILLIN AND MALARIAL FEVER TREATMENT IN CEREBROVASCULAR SYPHILIS (Report of a Case and Review of Literature) 55
Wallis L. Craddock, M.A., M.D., Fort Logan, Colorado

NEUROLOGICAL CLINICAL PATHOLOGICAL CONFERENCE 59

SANITARIA

ASSOCIATE EDITORS

A. E. Bennett, M.D. ..... Berkeley, California
Francis J. Braceland, M.D. ..... Rochester, Minn.
Franklin G. Ebaugh, M.D. ..... Denver, Colorado
Temple Fay, M.D. ..... Philadelphia, Pennsylvania
Milton H. Erickson, M.D. ..... Eloise, Michigan
Hamilton Ford, M.D. ..... Galveston, Texas
Walter Freeman, M.D. ..... Washington, D. C.
George T. Harding, M.D. ..... Columbus, Ohio
Jas. K. Hall, M.D. ..... Richmond, Virginia
A. Hauser, M.D. ..... Houston, Texas
Louis J. Karnosh, M.D. ..... Cleveland, Ohio
Frank H. Luton, M.D. ..... Nashville, Tennessee
Wm. Malamud, M.D. ..... Worcester, Mass.
Karl A. Menninger, M.D. ..... Topeka, Kansas
Adolf Meyer, M.D. ..... Baltimore, Maryland
Glenn Myers, M.D. ..... Los Angeles, California
Hans H. Reese, M.D. ..... Madison, Wisconsin
S. Bernard Wortis, M.D. ..... New York, N. Y.

Titus H. Harris, M.D.
Galveston, Texas
Editor-in-Chief

YEARLY SUBSCRIPTION $4.00
SINGLE COPIES 40 Cents
FOREIGN SUBSCRIPTION $4.50

George Biegeir, B.S., LL.B.
Chicago, Illinois
Managing Editor

68th Year

THE

RING SANATORIUM AND HOSPITAL

Arlington Massachusetts

Eight miles from Boston at an elevation of 400 feet

Specializing in the individualized care of Neuropsychiatric illnesses and Habit conditions. All accepted Therapies under the direction of a resident medical staff and trained assistants. Cottage plan permits a variety of accommodations.

VOLTA ROSS HALL, M.D.
Medical Director

HALLAM T. RING
Administrator

In conjunction: The Ring School of Attendant Nursing

HARDING SANITARIUM

WORTHINGTON, OHIO

For Nervous and Mental Disorders

NINE MILES NORTH OF STATE HOUSE — COLUMBUS

HARRISON S. EVANS, M.D., Medical Director
GEORGE T. HARDING, M.D., President of Board
CHARLES L. ANDERSON, M.D., Clinical Director

L. HAROLD CAVINESS, M.D.
J. RUSSELL FRANTZ, M.D.
THEODORE J. LUKENS, M.D.
LESLIE H. GOULD, M.D.
CHARLES W. HARDING, M.D.

Telephone: Columbus FR. 2-5367

Compton Sanitarium

AND

Las Campanas Hospital

COMPTON, CALIFORNIA
(Near Los Angeles)

Compton Sanitarium is a private psychiatric hospital with 120 beds. Emphasis is given psychotherapy by a staff of resident psychiatrists. Other treatment procedures are duly evaluated and administered. Careful records are maintained. There are psychiatrically trained graduate nurses; student nurses through affiliation; nursing attendants; dietitian; occupational therapist; recreational therapist; hydrotherapist; masseuse. Las Campanas Hospital (43 beds) provides adjunct general hospital facilities. Compton Sanitarium and Las Campanas Hospital are approved by the American College of Surgeons.

GLENN MYERS, M.D., *Medical Director.*

Beverly Hills Sanitarium

for

The Study and Treatment of Nervous and Mental Diseases

218 NO. WESTMORELAND DALLAS 11, TEXAS

This sanitarium is a psychopathic hospital with a home-like environment and is equipped to treat psychiatric and neurological cases in a most scientific manner by means of psychotherapy, occupational therapy, recreational therapy and physiotherapy, including insulin and electroshock treatments; electroencephalograph available.

ARTHUR J. SCHWENKENBERG, M.D.
Neuropsychiatrist
STEPHEN WEISZ, M.D.
Assoc. Neuropsychiatrist and Clinical Director

Staff Physicians
JANE N. CREEL, M.D.
E. C. WINKELMANN, M.D.

VOL. X FEBRUARY 1949 NO. 2

EDITORIAL OFFICES
UNIVERSITY OF TEXAS SCHOOL OF MEDICINE
800 Avenue B., Galveston, Texas

PUBLICATION OFFICE
PHYSICIANS POSTGRADUATE PRESS
277 Broadway, New York 7, New York

DISEASES of the NERVOUS SYSTEM

(PUBLISHED MONTHLY)

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Entropy, Mental Disease and Death

LEWIS DANZIGER, M.D.*
Wauwatosa, Wisconsin

I. Introduction

This study deals with a fundamental problem of pathology, namely the relation of age to disease and death. The following aspects of the question will be considered: Why does the death rate of the general population, so high during the first month of life, fall during later months of infancy and the early years of childhood, then begin to rise again and climb slowly to a maximum in old age? Why does the incidence of mental disorder increase with age? Why do psychiatric hospital patients have higher death rates at each year of age than are shown by the general population of the same age? The last question is especially puzzling if it is true that psychiatric patients or many of them have no "organic" or "physical" disability. Answers to these questions will be proposed from simple chemical considerations and will be shown to be consistent with thermodynamic principles.

It is futile to say that old people die rapidly because heart disease and cancer are common in the upper age brackets, or that mental patients are more susceptible than the general population to tuberculosis. Such statements do not tell us why old people are ready victims of heart disease and cancer or why mental patients are more susceptible (if they are) to tuberculosis. Such answers, by giving an appearance of definiteness, stifle inquiry and conceal ignorance. An approach at once more general and more precise will be used in the present investigation.

*Clinical Assistant Professor of Psychiatry, Marquette University.

Elsewhere[2] it has been suggested that a depression of cellular respiration is a sufficient and perhaps a necessary condition for mental disorders. This idea will now be extended to explain the incidence of mental disorders and to predict the age specific death rates of the general and psychiatric hospital populations. From this it will be shown that mental disease and death represent more probable conditions than health and life, that mental disease and death constitute situations of increased entropy or decreased free energy. Thence, it will follow that the alleviation of disease and the postponement of death will be accomplished by measures which increase the free energy of the patient.

In disorders not due to purely mechanical disturbances, e.g. severing of bones and other organs, obstructions in the gastro-intestinal and other tracts, and the like which require surgical interference, the abnormalities will in principle be treated by chemical means calculated to increase the free energy. The precise chemical treatment will, of course, depend on the nature of the offending agent.

II. Oxygen Consumption

Let us now consider some conditions necessary for cellular respiration. For oxygen to be consumed in the animal body, at least one reaction is necessary. This will be of the type

$$O_2 + [\text{red}] \longrightarrow [\text{ox}]$$

That is, a reduced compound (red) must be changed to the oxidized form (ox). Since ordinarily the supply of oxygen is very large,

the limiting factor determining the speed of the reaction will be the amount of the reduced acceptor [red]. We may then write that the rate of oxygen consumption, Q is proportional to red

$$Q = k\,[red] \qquad (1)$$

At all times [red] and [ox] will be determined by at least one equilibrium, since the oxygen acceptor must always be in either the reduced or the oxidized form, and since the reduced form is regenerated by the passage of the oxygen to a second acceptor. Choosing suitable units of measurement, we then have

$$[red] + [ox] = 1.0 \qquad (2)$$

It is assumed that the probability, P, of death or of mental disease will depend in some manner on this equilibrium, or on the ratio [ox]/[red]. That is,

$$P = f\,([ox]/[red]) \qquad (3)$$

The nature of this function will be determined experimentally. The advantage of considering the ratio rather than the value Q will appear in section V.

It is known[1,5,11] that the amount of oxygen consumed per unit time per unit surface area by the human body varies with age. The amount at birth is small, it increases rapidly to a maximum at about age 1.5 years, then declines rapidly to maturity, and thereafter more slowly to senility. The periods of decline are linear from age 5 years to maturity and linear (but with a different slope)

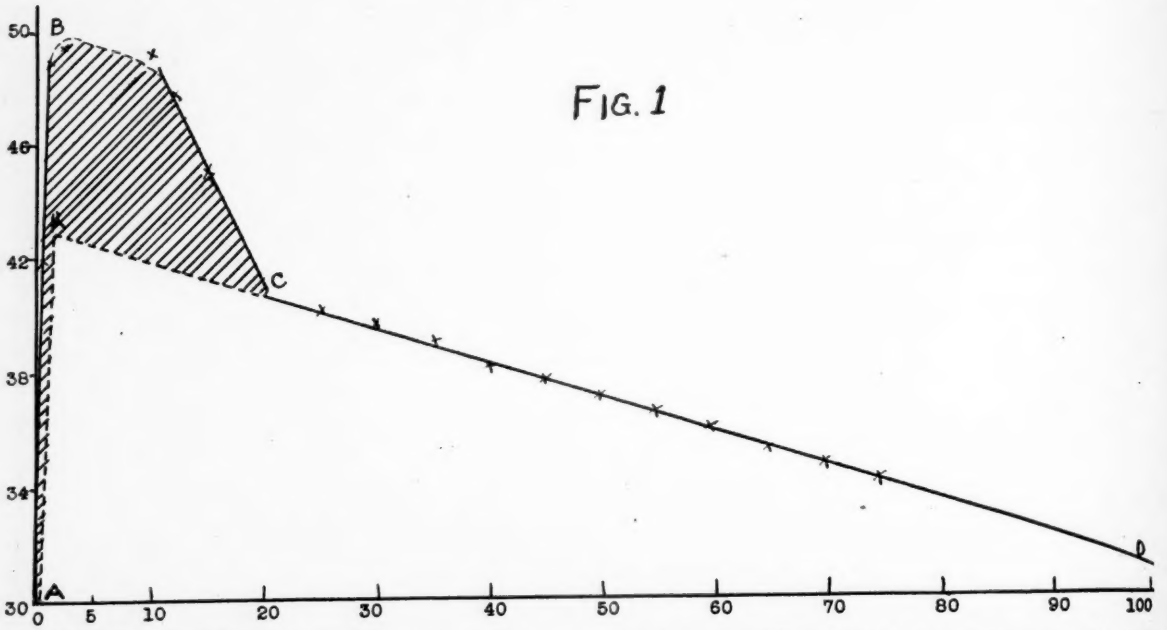

FIGURE 1: Relation of oxygen consumption per unit surface area per hour to age, in males. Ordinate, the rate of oxygen consumption. Abscissa, age in years. The shaded area represents the estimated cost of growth expressed in calories per square meter per hour.

FIGURE 2: Relation of age specific death rates of males in 1901 in the U. S. Registration Area to the ratio $K - Q/Q$.
Ordinate, death rates on logarithmic scale. Abscissa, ratio. Crosses, death rates under age 10. Circles, death rates at age 10 or more.

FIGURE 3: Same as Figure 2 except for 1939-41 for the United States.

FIGURE 4: Postulated eventual relation of age specific death rates to the ratio $K - Q/Q$.
Ordinate, death rates on logarithmic scale. Abscissa, the ratio. The death rates fall to a minimum at age 1.5 years.

FIGURE 5: Relation of age specific death rates of fruit fly to ratio 1 – [red]/[red].
Ordinate, death rates on logarithmic scale. Abscissa, the ratio.

FIGURE 6: Relation of age specific death rates of males of India, 1901-1910 to ratio 1–[red]/[red].
Ordinate, death rates on logarithmic scale. Abscissa, the ratio. Female death rates fall on the same curve.

FIGURE 7: Relation of approximate age specific death rates of male patients in state hospitals of the United States, 1939, to ratio $K - O.NQ/O.NQ$.
Ordinate, death rates on logarithmic scale. Abscissa, the ratio.

FIGURE 8: Relation of age specific rates of first admission of male patients to state hospitals in 1933 to the ratio $Q/(K-Q)$.
Ordinate, first admission rates on logarithmic scale. Abscissa, the ratio.

FIGURE 9: Probability of eventual recovery from manic-depressive psychoses treated symptomatically in state hospitals in 1933. Ordinate, probability of eventual discharge recovered. Abscissa, the quantity u, defined as a function of the duration of illness by equation (6). For original data see Danziger.[3]

FIGURE 10: Same as Figure 9 except data are for involutional psychoses.

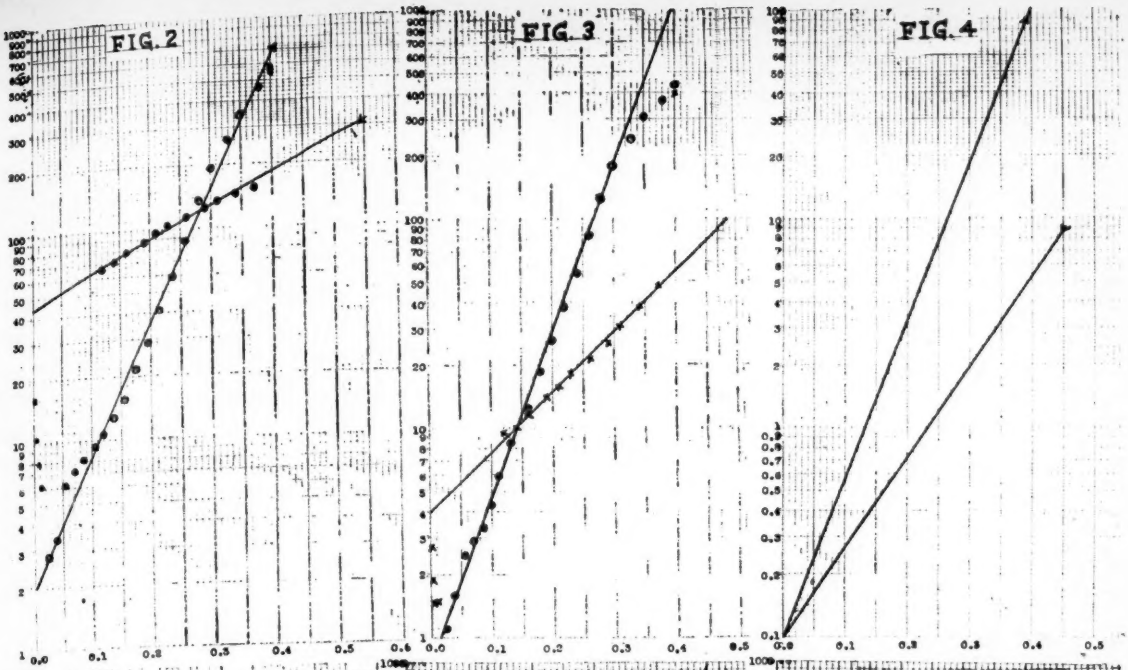
FIG. 2
FIG. 3
FIG. 4

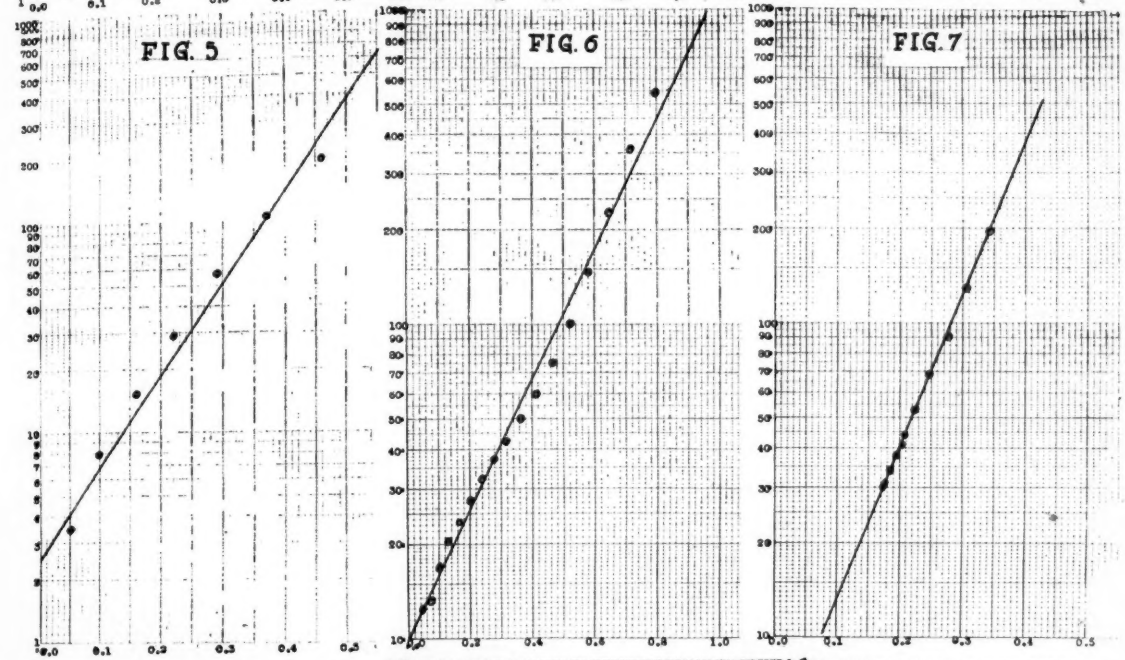
FIG. 5
FIG. 6
FIG. 7

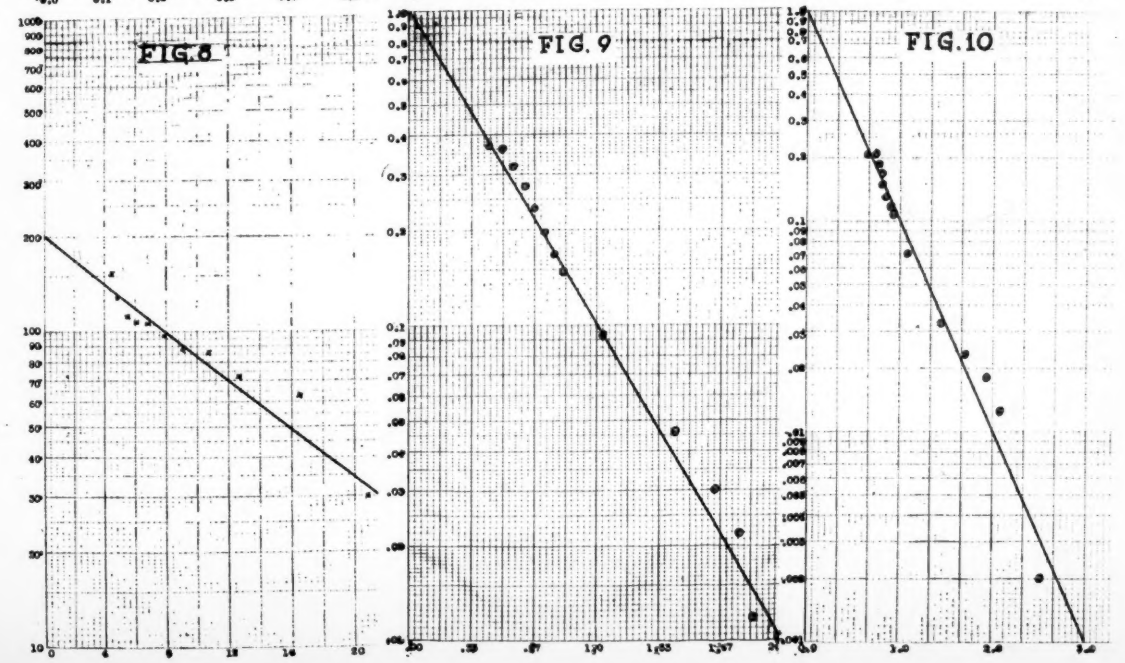
FIG. 8
FIG. 9
FIG. 10

from maturity to senility. Only a small error will be introduced by assuming the decline is linear from age 1.5 years to maturity, and that the increase from birth to 1.5 years is also linear. The experimental observations for males are given by the lines ABCD in Figure 1. Extrapolate the linear segment CD to its value at age 1.5 years, at point K. Draw AK. The area under ABCD minus the area under AKD, i.e. the shaded area in Figure 1, then represents approximately the cost of growth in terms of oxygen consumption per unit surface area per unit time. A similar graph may be constructed from the data for females.

Then BC intersects CD at age 20.5 years for males and at age 17 years for females. At these average ages, then, growth ceases.

The values given by AKD will be used for the determination of Q in equation (5). Thus, only the oxygen used for cellular activity aside from growth will enter into the calculations, at least after age 1.5 years. At earlier ages, the corrected Q values are perhaps too high by an unknown amount, though they are smaller than the observed values.

It is apparent that Q reaches a maximum at age 1.5 years, rising during infancy and falling thereafter. This rise and fall will reflect changes in [red] according to (1) and in the oxidation-reduction equilibrium according to (2) and (3).

Substituting (2) in (3) we obtain

$$P = f\ (1 - [red]/[red]) \qquad (4)$$

and substituting (1) in (4), we obtain, upon clearing fractions

$$P = f\ (K - Q/Q) \qquad (5)$$

Let K be numerically equal to the maximum Q, the rate obtaining when the amount of oxygen acceptor in the reduced state reaches its maximum, so that the fraction is never negative. The values for the ratio $K-Q/Q$ are given for males at various ages in Table 1 and for females in Table 2. These values will be used for the prediction of death rates.

III. Death Rates

Age specific death rates for the United States Registration Area of 1901, and for the United States in 1939-41 are plotted against the ratio $K-Q/Q$ in Figures 2 and 3. For ages less than 1 year, the monthly death rates are multiplied by 12. All death rates are from the United States Life Tables,[13] published by the Bureau of the Census from time to time. It is seen that the logarithm of the death rate is a linear function of the ratio from 1 month to 12 months and from 10 years to 104 years. A similar relation holds for females. Between 12 months and 9 years, the death rates are higher than the theory requires and between 1.5 years and 10 years they are declining rather than rising. The discrepancy between theory and observation is very much smaller in 1939-41 than in 1901, and the slopes have changed considerably in the interval. It is suggested that these changes reflect the progress of medicine in this 40 year period. Further advances in obstetrics and pediatrics may eventually cause such reductions in infant and child mortality that we will obtain Figure 4, with the minimum death rate at about 1.5 years. The excessive death rates for the first month of life are due mainly to deaths in the first few days. They probably reflect, therefore, obstetrical accidents and failure of normal development of the fetus.

Death rates of the general population are thus seen to be correlated with changing rates of oxygen consumption and with changes in the postulated oxidation - reduction equilibrium. Economic and climatic factors, the state of medical knowledge and the degree to which this knowledge is applied are expressed in the slopes of the curves.

The effect of these ecological factors is illustrated in the death rates for India in 1901-1910. In the very high death rates we see the expression of poverty and inadequate medical attention. The calculated ratios against which the rates are tabulated are probably in error because no correction was made for the effect of the warm climate, which is said to reduce the average Q. A means of surmounting this difficulty will be presented below, after a consideration of the life table of the fruit fly.

Such a table has been prepared by Pearl.[10] His data may be compared with human life tables by making certain assumptions, as follows:

1) One day for the fruit fly is roughly equivilant to one year for man;

2) [red] declines linearily with age from 1.0 at the beginning of adult life to 0.5 at 110 days.

Applying assumption 2 to equation (4) and

TABLE 1: Age Specific Death Rates and [ox]/[red] Ratio for Normal Male Population.

Age	Q in calories per square meter per hour*	Ratio	Annual death rate, 1901 per 1,000 living of same age and sex**	Annual death rate, 1939-41, per 1,000 living of same age and sex***
0-0.9 months	30.8	0.40	555.7	394.1
1-1.9	31.5	0.37	155.4	48.6
2-2.9	32.2	0.34	143.6	38.4
3-3.9	32.9	0.31	133.8	31.3
4-4.9	33.6	0.29	123.8	25.4
5-5.9	34.3	0.26	114.5	21.5
6-6.9	35.0	0.23	105.2	18.1
7-7.9	35.7	0.21	95.9	15.8
8-8.9	36.4	0.19	87.1	13.9
9-9.9	37.1	0.16	78.8	11.8
10-10.9	37.8	0.14	71.5	10.2
11-11.9	38.5	0.12	66.5	9.5
1.5 years	43.02	0.0000		
2-2.9	42.96	0.0014	16.1	2.7
3-3.9	42.84	0.0042	10.4	1.9
4-4.9	42.7	0.0069	7.9	1.5
5-5.9	42.6	0.011	6.1	1.5
10-10.9	42.0	0.024	2.8	1.1
15-15.9	41.4	0.039	3.4	1.6
20-20.9	40.8	0.054	6.1	2.5
25-25.9	40.2	0.070	7.2	2.9
30-30.9	39.6	0.087	8.1	3.4
35-35.9	39.0	0.10	9.4	4.3
40-40.9	38.4	0.12	10.7	6.0
45-45.9	37.8	0.14	12.8	8.6
50-50.9	37.2	0.16	15.6	12.6
55-55.9	36.6	0.18	21.5	18.5
60-60.9	36.0	0.20	28.8	26.5
65-65.9	35.4	0.22	41.4	37.6
70-70.9	34.8	0.24	59.1	54.8
75-75.9	34.2	0.26	88.5	82.8
80-80.9	33.6	0.28	133.6	123.9
85-85.9	33.0	0.30	191.2	178.3
90-90.9	32.4	0.33	262.0	241.7
95-95.9	31.8	0.35	349.0	306.5
100-100.9	31.2	0.38	461.8	371.5
104-104.9	30.7	0.40	575.1	432.4

*Corrected according to method described in text.

**Death rates for original registration states. For ages under 1 year, monthly death rates have been multiplied by 12.

***Death rates for United States. For ages under 1 year, monthly death rates have been multiplied by 12.

TABLE 2: Age Specific Death Rates and [ox]/[red] Ratio for Normal Female Population.

Age	Q in calories per square meter per hour*	Ratio	Annual death rate, 1901 per 1,000 living of same age and sex**	Annual death rate, 1939-41, per 1,000 living of same age and sex***
0-0.9 months	30.0	0.29	426.7	302.5
1-1.9	30.5	0.27	126.0	38.2
2-2.9	31.1	0.24	117.8	31.2
3-3.9	31.6	0.22	110.3	26.4
4-4.9	32.2	0.20	103.1	21.5
5-5.9	32.7	0.18	96.0	17.9
6-6.9	33.2	0.16	88.9	15.8
7-7.9	33.8	0.15	82.0	13.0
8-8.9	34.3	0.13	75.5	11.4
9-9.9	34.9	0.11	69.8	10.2
10-10.9	35.4	0.092	65.0	8.4
11-11.9	35.9	0.076	61.8	8.4
1.5 years	38.67	0.0000		
2-2.9	38.62	0.0013	15.2	2.4
3-3.9	38.54	0.0034	9.9	1.7
4-4.9	38.5	0.0057	7.7	1.4
5-5.9	38.4	0.0081	6.0	1.2
10-10.9	37.9	0.020	2.6	0.8
15-15.9	37.5	0.032	3.5	1.2
20-20.9	37.1	0.044	5.7	1.9
25-25.9	36.6	0.056	6.9	2.3
30-30.9	36.2	0.069	7.8	2.8
35-35.9	35.7	0.082	8.5	3.5
40-40.9	35.3	0.096	9.5	4.5
45-45.9	34.9	0.11	10.9	6.2
50-50.9	34.4	0.12	13.6	8.8
55-55.9	34.0	0.14	18.9	12.6
60-60.9	33.5	0.15	25.3	18.4
65-65.9	33.1	0.17	36.6	27.4
70-70.9	32.7	0.18	53.8	42.7
75-75.9	32.2	0.20	80.5	68.6
80-80.9	31.8	0.22	120.9	106.9
85-85.9	31.4	0.23	174.0	159.3
90-90.9	30.9	0.25	243.9	223.0
95-95.9	30.5	0.27	332.1	290.2
100-100.9	30.0	0.29	445.6	353.7
104-104.9	29.7	0.30	562.0	406.9

*Corrected according to method described in text.

**Death rates for original registration states. For ages under 1 year, monthly death rates have been multiplied by 12.

***Death rates for United States. For ages under 1 year, monthly death rates have been multiplied by 12.

TABLE 3: Age Specific Death Rates and Postulated [ox]/[red] Ratio for Fruit Fly

Age in days	[red]	[ox]/[red]	Death rate per 1,000 living of same age
0	1.000	0.00	
10	0.955	0.05	3.5
20	0.910	0.10	7.9
30	0.865	0.16	15.1
40	0.820	0.22	29.1
50	0.775	0.29	56.9
60	0.730	0.37	109.2
70	0.685	0.46	199.4
80	0.640	0.56	338.7
90	0.595	0.68	
100	0.550	0.82	
110	0.505	0.98	

setting K=1.0 we obtain the ratios shown in Table 3 and plotted against the fruit fly death rates in Figure 5. Since the fruit flies have no known infant mortality problem, the data fall on a single straight line. While the fruit flies had an adequate supply of food and presumably lived under satisfactory climatic conditions in the laboratory, they had no medical attention. Their death rates are, perhaps for this reason, high and are not unlike those for India.

New K−Q/Q ratios for India have been calculated in a manner similar to that used for the fruit fly. It is assumed that in India [red] declines linearily from a maximum value at age 1.5 years to 101.5 years. Let the value of [red] at 1.5 years be unity and equal to K; and let the value of [red] at 101.5 years be 0.5. Assuming that Q is proportional to [red], we obtain the ratio values shown in column 3 of Table 4 without having to know the absolute values of Q.

TABLE 4: Age Specific Death Rates and Postulated [ox]/[red] Ratio for Normal Population of India, 1901-1910.

Age in years	[red]	[ox]/[red]	Annual death rate per 1,000 living of same age and sex, males	Annual death rate per 1,000 living of same age and sex, females
1.5	1.0000	0.0000		
10-10.9	0.9575	0.0445	12.5	12.9
15-15.9	0.9325	0.0725	13.2	13.4
20-20.9	0.9075	0.102	16.9	17.0
25-25.9	0.8825	0.133	20.3	20.0
30-30.9	0.8575	0.166	23.5	23.1
35-35.9	0.8325	0.202	27.8	26.6
40-40.9	0.8075	0.239	32.3	30.8
45-45.9	0.7825	0.278	37.2	35.3
50-50.9	0.7575	0.320	42.8	40.6
55-55.9	0.7325	0.366	49.9	47.4
60-60.9	0.7075	0.414	59.8	57.8
65-65.9	0.6825	0.465	75.5	74.4
70-70.9	0.6575	0.522	101.7	101.2
75-75.9	0.6325	0.581	148.0	146.0
80-80.9	0.6075	0.646	228.7	224.9
85-85.9	0.5825	0.718	366.3	362.8
90-90.9	0.5575	0.795	545.5	590.7
95-95.9	0.5325	0.880		
100-100.9	0.5075	0.970		
101-101.9	0.5000	1.000		

The plot of this set of values of the ratio against the Indian death rates as shown in Figure 6 gives a better fit than was obtained when the American ratios were used.

Patients in state psychiatric hospitals have age specific death rates which are much higher than those of the general population. This phenomenon is difficult to explain if it is assumed that psychiatric patients have no "organic" or "physical" disability. Hospitalized patients are provided with reasonably adequate food, clothing, housing and medical attention. They are protected against traffic accidents, occupational and venereal diseases, pregnancy and exposure. Serious accidents in the hospital industries (laundry, kitchen, housekeeping and farm) are unusual. The patients have adequate plumbing facilities. They are encouraged to eat and sleep at regular hours. Whence, then, the extremely high death rates?

It is known from direct measurement[7] that many psychiatric patients have low Q values. It is reasonable to suppose also from indirect evidence that low Q values are common, if not almost universal, among the patients. For example, the Q may be reduced in the psychiatric patients by numerous drugs and poisons commonly used in medicine and industry;[2] by vitamin deficiency diseases when these are accompanied by impairment of respiratory enzymes; by spontaneous hypoglycemia; by heart failure; by syphilis (with damage to the iron containing respiratory enzymes);[6] by thyroid deficiency; by arteriosclerosis, and so on.

Let us assume that in the state psychiatric hospital population, Q is reduced to some lower value O.NQ. If we set N=9 and plot the ratios K−O.NQ/O.NQ against the death rates, we obtain only a poor fit. The theory then predicts death rates which are lower than observation at ages 18, 22, 27, 62 and 67, and higher than observation at ages 42, 47, 52, 57. This could be because of the small number of observations (about 15,000 for women and 20,000 for men). But it could also be because the factor 9 is not applicable to all ages. This view is in accord with clinical judgment, which gives a poor prognosis in young (schizophrenic) and old (late involutional and arteriosclerotic) patients and a better prognosis in middle-aged (manic depressive and early involutional) patients. The same variation in prognosis holds if shock therapy is given in the several age groups.

Slight changes in the value of N from age to age will bring the death rates into line. Making these changes, we obtain Table 5 and 6. The data for males are shown in

TABLE 5: Age Specific Death Rates and Postulated [ox]/[red] Ratio for Male State Hospital Population, 1939

Age in years*	N**	Ratio	Deaths per 1,000 of same age and sex under treatment
15-19	8.65	0.185	34
20-24	8.82	0.175	31
25-29	8.95	0.172	30
30-34	8.95	0.192	38
35-39	9.00	0.204	41
40-44	9.10	0.208	44
45-49	9.35	0.225	53
50-54	9.10	0.248	69
55-59	9.05	0.277	91
60-64	9.00	0.305	128
65-69	9.15	0.341	196

*Death rates for single years are not available. It is assumed the deaths occurred at ages 18, 22, 27, 32, 37, 42, 47, 52, 57, 62, and 67.

**Unweighted mean value of N is 9.01.

TABLE 6: Age Specific Death Rates and Postulated [ox]/[red] Ratio for Female State Hospital Population, 1939

Age in years*	N**	Ratio	Deaths per 1,000 of same age and sex under treatment
15-19	8.60	0.210	38
20-24	8.80	0.195	33
25-29	8.90	0.195	33
30-34	9.00	0.195	33
35-39	9.00	0.206	37
40-44	9.10	0.206	37
45-49	9.15	0.216	41
50-54	9.15	0.235	52
55-59	9.10	0.255	64
60-64	8.95	0.289	92
65-69	8.90	0.325	137

*Death rates for single years are not available. It is assumed the deaths occurred at ages 18, 22, 27, 32, 37, 42, 47, 52, 57, 62, and 67.

**Unweighted mean value of N is 8.97.

Figure 7; a similar correlation is obtained on plotting the data for females. It is apparent that the unweighted mean value of N is indeed about 9, corresponding to a mean basal metabolic rate of about minus 10 per cent.

The very high death rates shown in the tables should be remembered by those who are alarmed by the risks of shock therapy. They should remember that while electric shock therapy is about as dangerous as a tonsillectomy, the expectation of life in untreated psychiatric hospital patients is about one half normal.[9] Those who cling to the idea that psychiatric disabilities are "functional" or "not physical" sometimes appear to forget that the patients die as if they are suffering from some serious disease. Those who withhold shock therapy in manic-depressive psychoses on the ground that the illness is usually self-limited, sometimes appear to forget that in one-third of the untreated state hospital cases the illness becomes self-limited only at death.[14]

IV. Incidence of Mental Disorder

The increasing incidence of psychiatric disorders with advancing age may also be correlated with the decline in Q values. For reasons which will appear later, attention is confined to first admissions to state hospitals as reported to the Bureau of the Census.

While behavior problems are common in childhood, they rarely require hospital treatment in persons under age 13 years, and admissions of persons under age 15 years are unusual. Thus, although the psychiatrically disabled population may have reduced Q values, the amount of the reduction at age 13 is rarely sufficient to produce a disability requiring hospital treatment. At age 13, Q or O.NQ is therefore sufficiently large to prevent admission. As age increases and Q declines, the admission rates increase at first rapidly, then more slowly in middle life, then rapidly again in old age.

As in the preceeding sections, the relation of Q to the rate is determined experimentally. It turns out that the logarithm of the first admission rate is a linear function of the reciprocal of the ratio K−Q/Q with a negative slope. The data are shown in Tables 7 and 8 and those for males in Figure 8.

It is necessary first, however, to say some things about the Census data. For the years 1933 and 1943 and for some of the years between, the Census reports by age and sex the first admissions to public and private institutions for the permanent and temporary care of patients with disorders of behavior.[14,15] Certain difficulties are present in the figures and are recognized by the Census workers.[12] The data are tabulated by clerks in the various reporting institutions and the tables are sent to Washington for further processing. The clerks are given written instructions defining the term "first admission" to permanent-care hospitals as "patients admitted without a record of previous admission to or discharge from that, *or any other*, permanent-care hospital," (italics mine). Following the italicized instruction requires, in some cases, close examination of the individual records of the patients. It is not reasonable to suppose that the low salaried clerks, burdened with their ordinary routine duties, will take this precaution in every case or even in many cases merely to satisfy the whim of a person they may regard as an arbitrary bureaucrat in far away Washington. It is more reasonable to picture the

TABLE 7: Age Specific Rates of First Admission to State Hospitals, 1933, Male Patients; and [red]/[ox] Ratio

Age in years*	First admissions per 100,000 of same age and sex of general population at nearest decennial census	Ratio**
15-19	30	20.8
20-24	63	16.4
25-29	73	12.6
30-34	86	10.7
35-39	87	9.1
40-44	97	7.9
45-49	106	6.9
50-54	107	6.1
55-59	112	5.5
60-64	128	4.9
65-69	153	4.5

*Admission rates for single years of age are not apailable. It is assumed the admissions occurred at ages 18, 22, 27, 32, 37, 42, 47, 52, 57, 62, and 67. Admission rates at ages 70 and over are not completely broken down, some institutions not reporting admissions by age after age 70.

**With K = 43.02 and Q obtained by interpolation from Table 1.

clerks interpreting "first admission" as "first admission to our hospital" which permits speedy completion of the appointed task. There must, therefore, be some excess in the figures; some reported first admissions must be really re-admissions.

Attention is confined to the state hospital figures because it is believed this reduces the reporting error to some extent. The state hospitals serve the largest section of the population, most of which has never been able to afford private psychiatric hospital care. At least until the advent of shock therapy, and the growth of the veterans hospitals, the state hospital populations were relatively stable. There was less movement of patients from hospital to hospital and, because of the poor prognosis on first admission, there was less chance for a second admission.

For these reasons, the figures for 1933 are believed to be especially reliable. In 1933, only about 1800 first admissions were reported by the veterans hospitals, but by 1943 this number had increased to more than 12,000. Since the veterans are admitted on a voluntary basis, there is considerable migration from hospital to hospital as the patients become restless and dissatisfied. It is probably true that all admission rates depend in part on the diagnostic and treatment facilities avaialble. These facilities were expanded very rapidly after 1940 with the growth of the military establishment. Between 1940 and 1943, millions of men of military age were exposed for the first time to reasonably adequate psychiatric attention in situations which in themselves may have contributed to psychiatric disability. Under these conditions, a sudden increase in first admission rates among men of military age would not be surprising, and was in fact reported by the veterans hospitals. At the same time there was a decrease in first admissions of men of military age to the state hospitals during these years.

Between 1933 and 1943, only a negligible number of women were eligible for study by the military psychiatrists or for veterans hospital care; their admission rates were therefore not affected by the expansion of the federal facilities in this interval. When the data for women for 1944 and later years become available, some distortion may be expected in the military age groups as the female veterans begin to enter the federal hospitals in large numbers.

For these reasons it is impossible to compare the admission rates for men for 1933 and later years (the next available year is 1939). The admission rates for women, during

TABLE 8: Age Specific Rates of First Admission to State Hospitals, 1933, 1939, 1940, 1941, 1942 and 1943, Female Patients; and [red]/[ox] ratio.

Age in years*	First admissions per 100,000 of same age and sex of general population at decennial census nearest decennial census							
	1933	1939	1940	1941	1942	1943	mean	Ratio**
15-19	22	24	23	25	25	24	24	27.9
20-24	42	42	41	45	45	40	43	20.4
25-29	54	57	58	59	56	50	56	16.4
30-34	64	66	64	68	72	62	66	13.5
35-39	67	74	70	75	69	65	70	11.4
40-44	74	74	70	73	74	69	72	9.9
45-49	79	76	74	80	72	70	76	8.7
50-54	78	81	80	83	84	79	81	7.7
55-59	77	82	79	87	84	80	82	6.9
60-64	88	82	86	87	93	93	88	6.3
65-69	100	98	100	115	114	123	108	5.7

*Admission rates for single years are not available. It is assumed the admissions occurred at ages 18, 22, 27, 32, 37, 42, 47, 52, 57, 62 and 67. Admission rates at ages 70 and over are not completely broken down, some institutions not reporting admissions by age after age 70.

**With K = 38.67 and Q obtained by interpolation from Table 2.

the period 1933 to 1943, on the other hand, are comparable and are found to be very stable. Figures for the private institutions are excluded from this study because of the probable reporting error mentioned above.

The data plotted in Figure 8 and shown in Tables 7 and 8 are for all first admissions regardless of diagnosis and including those patients said to be without psychosis. All the patients, however, must have shown behavior sufficiently disturbing to themselves and to others to bring them to the attention of state hospital psychiatrists. In the present state of our knowledge of the pathogenesis of such behavior, it may be premature to make distinctions between various nosological groups. There seems general agreement that the psychopath has a disability of some kind which may be quite as incapacitating as catatonia. Whether both groups are suffering from impaired cerebral metabolism, which may be caused in a hundred different ways, no one knows. The figures now available appear only to indicate that first admissions to state hospitals obey a simple law.

In another study,[4] it was shown that patients recover from dementia praecox when receiving symptomatic treatment in state hospitals in accordance with an equation which was interpreted as suggesting a change in cerebral metabolism. In Figures 9 and 10, it is shown that patients given symptomatic treatment in state hospitals in 1933 for manic-depressive psychoses and involutional psychoses recover in accordance with the same law which appears to govern the recovery from dementia praecox. That is, the prognosis in each of these nosological groups is determined by assuming the disorder is caused by a hypothetical substance, u, of which the rate of increase is given by

$$du/dt = a - bu \qquad (6)$$

where a is the rate at which the material is added to the body and bu is the rate at which it is destroyed or excreted. The values of a and b, respectively, in the three groups are:

dementia praecox: 0.077 and 0.027
manic depressive psychoses: 0.080 and 0.040
involutional psychoses: 0.054 and 0.020

If these three types of disorder seem to obey the same theoretical law of pathogenesis, it is possible that all types of mental disorder have, in general, a common type of origin. Qualitative evidence in support of this view has already been presented.[2]

It is for these reasons that all types of mental disorder, whether or not associated with a psychosis, are lumped together in Tables 6 and 7 and Figure 8. Clinical evidence also suggests this course. For example, the delusions and confusion which are attributed in elderly patients to senility or arteriosclerosis, are not too different from the same symptoms which in younger patients are attributed to dementia praecox, involutional changes, alcoholism or drug intoxication. The presumed cause and clinical diagnosis will be determined all too often by the patient's age. The good response to shock therapy by so many patients of different nosological groups also must eventually decrease the rigidity of the Kraepelin system.

Whether this view is correct or not, future experiment will decide. For the present it is suggested from the evidence in this paper and from others already referred to that attention be given to the cerebral metabolism, and in particular that a search be made for materials and methods which will

1) Increase the amount of available respiratory enzyme, as postulated; this type of therapy is already available in delirium tremens and other diseases due to avitaminosis B.

2) Release from inhibition the respiratory enzymes already present in the patient; this type of therapy, in the form of British antilewisite, is already available for patients poisoned by arsenic or mercury.

V. Thermodynamic Considerations

The importance and utility of the [ox]/[red] ratio having been demonstrated, let us now consider some possible thermodynamic aspects of the problem. The notation used in this section is that of Lewis and Randall.[8] It is difficult to see how the postulated oxygen acceptor can be anything but a respiratory enzyme. The oxidation-reduction potential, E, of this system will then be given by

$$E = E_0 + RT/nF \ln [ox]/[red] + RT/F \ln \sqrt{H_2 \text{ pressure}}/[H+]$$

where E_0 is the potential under some standard conditions, R is the gas constant, T the absolute temperature, n the electrons exchanged,

F the faraday. Assuming constant pH, the last term will have no influence in the body, and the potential will be determined at a given temperature by the [ox]/[red] ratio. As the ratio increases in value, the free energy of the system will decline in accordance with

$$-\Delta F = nFE$$

where ΔF is the change in free energy. If the postulated oxidation is like most chemical reactions, the decrease in free energy will be accompanied by an increase in entropy.

The [ox]/[red] ratio is hence an indirect measure of entropy, and an increasing ratio means an increasing entropy. According to this analysis, then, the average entropy of the population falls to a minimum at age 1.5 years and rises thereafter. During this process, some sensitive members of the population will be unable to tolerate the increase in entropy or will increase in entropy either suddenly or more rapidly than normal and will develop psychiatric disabilities. Such disorders are thus seen to be states of increased probability, just as death is a more probable state than life, in accordance with

$$Sb - Sa = R/N \ (\ln Pb - \ln Pa)$$

the Boltzman equation, where S is the entropy. Left to itself, the population then drifts toward the mental hospital and the grave.

Spontaneous recovery from mental disorders serious enough to require hospitalization should therefore be expected to be uncommon. That this is true is already known[3] from a study of Census reports and by the experience of most hospital psychiatrists.

This analysis suggests in very general terms the appropriate measures to be taken for the alleviation of mental disorders and the postponement of death. The entropy of a system can be decreased only at the expense of work done by another system, unless we are willing to await the rare chance decreases predicted by the Boltzman equation. When the boiling of water or the cooling of a refrigerator is involved, we do not rely on this equation for our results. Perhaps in dealing with disease we should be equally impatient. The nature of the chemical work which will succeed in psychiatry and in other medical specialties will depend, naturally, on kinetic considerations. If, for example, the difficulty is in one of the cytochromes, no relief is to be expected from increasing the hemoglobin. If niacin is needed, thiamin will not do. For the solution of these kinetic problems we must await the help of the biological chemists.

VI. Summary and Conclusions

In this study attention is called to the fall of age specific death rates during infancy and childhood and to the rise of the rates in later life. These rates are shown to be correlated with the standard rate of oxygen consumption. It is postulated that the rate of oxygen consumption will depend on the presence in appropriate amounts of a suitable oxygen acceptor which forms part of a reversible oxidation-reduction system. This assumption leads to an equation, partly rational and partly empirical, which predicts the age specific death rates from birth to senility for man and which applies also to the fruit fly.

By assuming a depression of the rate of metabolism in psychiatric patients (an assumption supported by some experimental evidence), the equation is changed in a manner such that the age specific death rates of state psychiatric hospital patients can be predicted. A related equation predicts the age specific rates of first admission to state hospitals.

The postulated changes in the state of the oxidation-reduction system suggest changes in the average free energy and entropy of the general and psychiatric hospital populations. These changes are such that mental disease and death become increasingly probable at certain ages. Hence spontaneous recovery from psychiatric disability is seen to be unlikely, in accordance with observation, and the postponement of death is seen to be unlikely. However, these probabilities can be altered, in principle, by the expenditure of work which will decrease the average entropy of the population. The work will be performed by introducing sources of chemical energy into the patients. Appropriate sources of this energy will be defined by kinetic considerations, two of which are mentioned in connection with vitamin deficiency diseases and inactivation of sulfhydryl respiratory enzymes.

REFERENCES

1 Boothby, W. M .and Sandiford, I.: "Normal Values of Basal or Standard Metabolism," *Am. J. Physiol.*, 90:290, 1929.

2 Danziger, L.: "Anoxia and Compounds Causing Mental Disorders in Man," *Dis. Nerv. Syst.*, 6: 365, 1945.
3 Danziger, L.: "Prognosis in Some Mental Disorders," *Dis. Nerv. Syst.*, 7:229, 1946.
4 Danziger, L.: "Some Theoretical Considerations of Dementia Praecox," *Dis. Nerv. Syst.*, 7:357, 1946.
5 DuBois, E. F.: "Basal Metabolism in Health and Disease," *Lea and Febiger*, Phila., 1936.
6 Hoagland, H. in J. Alexander's "Colloid Chemistry," *Reinhold Pub. Co.*, New York, 1944.
7 Hoskins, R. G.: "Oxygen Consumption ('Basal Metabolic Rate') in Schizophrenia; Distribution in 214 Cases," *Arch. Neurol. and Psychiat.*, 23:1346, 1932.
8 Lewis, G. N. and Randall, M.: "Thermodynamics," *McGraw Hill Book Co.*, New York, 1923.
9 Malzberg, B.: "Social and Biological Aspects of Mental Disease," *State Hospitals Press*, Utica, N. Y., 1940.
10 Pearl, R.: "Medical Biometry and Statistics," *W. B. Saunders Co.*, Philadelphia, 1930.
11 Talbot, F. B.: "Standards of Basal Metabolism in Normal Infants and Children," *Am. J. Dis. Child.*, 21:519, 1921.
12 Truesdell, L. E.: Personal communication, 1946.
13 U. S. Bureau of the Census: "U. S. Life Tables," *Gov't. Print. Office*, Washington, D. C.
14 U. S. Bureau of the Census: "Patients in Hospitals for Mental Disease, 1933," *Gov't. Print. Office*, Washington, D. C.
15 U. S. Bureau of the Census: "Patients in Mental Institutions, 1939, 1940, 1941, 1942, 1943," *Gov't. Print. Office*, Washington, D. C.

Author's Note: The expenses of this investigation were defrayed, in part, by the Ada P. Kradwell Memorial Foundation.

Phenurone in Epilepsy

FREDERIC A. GIBBS, M.D., GUY M. EVERETT, Ph.D.
and R. K. RICHARDS, M.D.
Chicago, Illinois

A screening technique utilizing electroshock and metrazol convulsions in mice has shown that phenacetylurea (Phenurone) greatly raises the threshold or completely suppresses both types of convulsion.[1] Acute and chronic toxicity tests on dogs, cats and rats showed that the substance has a low toxicity. The lethal dose-50 (i.e. 50 out of 100 animals died) was found to be 3 to 5 grams per kg. in all species tested.

The clinical usefulness of Phenurone was tested on a group of 90 epileptic patients of different types. All had been found resistant to phenobarbital, Dilantin, Mesantoin, Tridione and Sodium 5, 5-phenyl thienyl Hydantoin (Thienyl Hydantoin). Fifty per cent of this group were not significantly improved (Table I) on Phenurone and fifty per cent were rendered seizure free or greatly improved for periods ranging from one to six months. The action of the drug seemed to be about equal against the three major types of seizures. Its effect against psychomotor seizures is impressive because such seizures are relatively little affected by Dilantin, which has its major action against grand mal, and Tridione which has its major action against petit mal (Table II). The average dosages that were employed are shown in Table III. If benefit did not result with moderate amounts (3.5 grams), higher dosage was usually ineffective. This drug is quickly eliminated so that in order to maintain a therapeutic level the dose should be fairly evenly distributed over the day. Phenurone is tasteless and in one psychotic patient it has been given in the food without difficulty.

The commonest side effect was weakness and anorexia. The latter was in some instances helped by the addition of Vitamin B Complex to the diet. However, the complication most often seen (in the present series) was exaggeration of the pre-existing personality disturbances that are often an accompaniment of psychomotor epilepsy.[2,3] The psychiatric manifestations of psychomotor epilepsy are varied. In any given case, however, the aberrations of behavior and character are fairly constant. In one patient they may resemble hysteria; in another,

From the University of Illinois College of Medicine, Department of Psychiatry and the Illinois Neuropsychiatric Institute, Chicago, Illinois and the Department of Pharmacology, Abbott Research Laboratories, North Chicago, Illinois.
Read before the meeting of the American Branch of the International League Against Epilepsy, June 13, 1948, Atlantic City, N. J.

schizophrenia, and in another, psychopathy. Strangely enough, there is little in the way of aberrations of sexual behavior. For the purpose of the present study, all psychiatric symptoms were listed under the heading of "personality disturbances." As will be seen in Table IV, an increase in personality disturbances was the most prevalent limiting side effect in the present series. The incidence of this side effect depends on the commonness of pre-existing personality disturbances in the group under study, for in no case without prior personality disturbances or psychiatric symptoms was a significant degree of personality disorder precipitated with Phenurone. It should be noted that although Phenurone commonly increases psychiatric disorders, a few patients while on this drug showed a great improvement in their psychiatric symptoms.

TABLE I

Total number of patients tried on drug	90
Not significantly improved	50%
Seizure free or greatly improved	50%
Discontinued	41%
Continued	59%

TABLE II

Type of Seizure	Number of Cases*	Greatly Improved** Number	Per Cent
Grand mal	35	11	33
Petit mal	15	7	46
Psychomotor	58	29	50

*A few cases with both grand mal and petit mal, or with psychomotor seizures and grand mal appear twice in the present table.

**Refers to the percentage of cases with a particular type of seizure in which the number of such seizures was greatly reduced.

TABLE III

PHENURONE DOSAGE FOR ADULTS

Minimum Effective Dose:
3 tabs. 0.5 grams (1.5 grams)
Average Dose:
5 tabs. 0.5 grams (2.5 grams)
Maximum Dose:
10 tabs. 0.5 grams (5.0 grams)

TABLE IV

LIMITING SIDE EFFECTS

Exaggeration of personality disturbances	20%
Anorexia	12½%
Feeling of weakness	6%
Headache	6%
Insomnia	6%
Palpitation	2½%
Rash	1%

Although personality disturbances were usually exaggerated only when and if psychomotor seizures were controlled, a few cases were encountered in which personality disturbances flared up even though the seizures continued. This suggests that the ictal and non-ictal symptomatology of psychomotor epilepsy are independent or even antagonistic. In some cases the maintenance of the patient in a seizure-free condition was undesirable because severe psychiatric symptomatology developed whenever seizures were controlled. On withdrawing Phenurone, seizures usually recurred promptly and the personality disorder subsided forthwith. In one case, however, this did not occur. Prior to treatment the patient had a mild personality disturbance with almost daily seizures. When these seizures were checked with Phenurone a severe psychotic state developed with auditory hallucinations and delusions of persecution. On discontinuing the Phenurone seizures did not recur. The mental status of the patient was not improved by electro-shock therapy, but seizures returned and the mental disorder diminished to the pre-Phenurone level after sub-shock insulin therapy. It has been observed that other anti-epileptic substances, for example, Dilantin, Mesantoin and phenobarbital, may similarly increase mental disorder in patients with psychomotor epilepsy; i.e., they may stop the epileptic seizures but aggravate the non-ictal psychiatric symptomatology. Phenurone appears to differ from other anti-epileptic substances not so much in kind as in degree. Its undesirable psychiatric side effects seem to be proportionate to its power to control psychomotor seizures.

Many patients on being started on Phenurone complain of insomnia. This can be counteracted by the use of phenobarbital or Mesantoin. At times these drugs also seem to give additional control of seizures. However, some cases have been encountered in which the addition of phenobarbital or Mesantoin reduced the therapeutic effect of Phenurone. Wherever possible the effectiveness of the Phenurone alone should be determined and any additional substances should be added as a second step.

In one case jaundice developed and on withdrawal of the Phenurone, subsided. Re-

institution of Phenurone-medication resulted in the reappearance of jaundice. It would appear that in this case at least a liver disturbance was produced by Phenurone. In only two cases were urinary changes found; both developed casts, blood and albumin in the urine. Shortly after discontinuation of the Phenurone the urinary examination gave normal findings.

In the series of patients upon which this paper is based only one per cent developed rashes. Since this preliminary report was prepared, Lennox has had several cases which have developed a rash and fever on Phenurone.[4] As with any new drug one must be on guard against blood damage; none has thus far been detected in our series.

Summary and Conclusions

Phenacetylurea (Phenurone) has been shown to possess superior anticonvulsant properties against both electro-shock and metrazol convulsions in animals and is a drug of low toxicity.

This drug is an important addition to the therapeutic agents that are used for the treatment of epilepsy, for it will in some cases control seizures that are not controlled by any other medication. In the present series it was found useful against all types of seizure and was uniquely effective against psychomotor seizures. Phenurone may be used alone or in combination with Mesantoin or phenobarbital. The chief limiting side effect is the intensification of pre-existing personality disorders. It should be used with caution in such cases. Since Phenurone can increase the non-ictal psychiatric symptomatology while reducing the ictal or purely epileptic component, it reveals an antithesis between these two components.

Author's Note: This research was aided by a grant from the Rockefeller Foundation and by contributions made specifically for this purpose to the Illinois Epilepsy League.

REFERENCES

1 Everett, G. M. and Richards, R. K.: "Pharmacological Studies of a New Anticonvulsant, Phenacetylurea (Phenurone)," In preparation.

2 Gibbs, Erna L., Fuster, Bartolome and Gibbs, Frederic A.: "Psychomotor Epilepsy," *Archives of Neurol. and Psychiat.* (In Press).

3 Gibbs, Frederic A. and Gibbs, Erna L.: "Psychiatric Implications of Discharging Temporal Lobe Lesions," *Transactions of the American Neurological Association.* (June 16, 1948).

4 Lennox, W. G.: Personal communication.

INTERNATIONAL CONGRESS OF PSYCHIATRY

An International Congress of Psychiatry is planned to be held in Paris on October 4th to 12th, 1950.

In accordance with regulations decided on at the International Preparatory Meeting (Paris, October 23rd, 1947) the official spoken languages will be: English, French, Spanish and (should Russia participate) Russian.

The proposed program of the six main afternoon sessions is the following:

(1) *General Psychopathology:* Session's Chairman, Professor Ferdinand Morel (of Geneva, Switzerland). Subject: *Psychopathology of Delusions.*

(2) *Clinical Psychiatry:* Session's Chairman, Porfessor Honorio Delgado (Lima, Peru). Subject: *Application of Testing Methods to Clinical Psychiatry.*

(3) *Psychiatric Anatomo - Physiology:* Session's Chairman, Professor F. L. Golla (Bristol, England). Subject: *Cerebral Anatomy and Physiology in the Light of Lobotomy and Topectomies.*

(4) *Psychiatric Biological Therapy:* Session's Chairman, Professor Jozef Handelsman (Warsaw, Poland). Subject: *Respective Indications of the Shock Therapy Methods.*

(5) *Psychotherapy, Psychoanalysis, Psychosomatic Medicine:* Session's Chairman, Dr. Franz Alexander (Chicago, U.S.A.). Subject: *The Evolution and Present Trends of Psychoanalysis.*

(6) *Social Psychiatry:* Session's Chairman, Professor Torsten Sjogren (Stockholm, Sweden). Subject: *The Genetic and Eugenic Aspects of Psychiatry.*

In each country, a National Committee of the Congress is being set up; when possible, a Chairman, a Secretary, and a Director are appointed for each section.

The Use of Sodium Amytal and Benzedrine Sulfate in the Symptomatic Treatment of Depressions*

JACQUES S. GOTTLIEB, M.D.
Iowa City, Iowa

The purpose of this report is to indicate the usefulness of the combination of sodium amytal (sodium iso amylethyl-barbiturate) and benzedrine sulfate (racemic amphetamine sulfate) in the treatment of patients with primary depression (manic-depressive type, and involutional psychosis, melancholia).

Sodium amytal, since the report of Lindemann in 1931,[1,2] has been known to have a temporary ameliorating effect upon the symptoms of depression. It is an effective anti-depressant. He demonstrated that this drug administered intravenously in subnarcotic doses produced a reaction in which the symptoms lessened in severity and the patient more closely approached his normal. The depressed mood may become affected in one of two ways. The more common response was for the depression to subside, the patient feeling more comfortable, pleasant, alert and even on occasion euphoric. The less common response was for the depression to become felt more strongly and expressed more overtly. In those in whom the emotional state shifted along the depression-elation scale in the direction of elation, other changes became apparent. Slowness in the mental processes, as thinking and communication, became less prominent. There developed a desire to communicate personal problems and experiences. Either slowness in movement or agitation, whichever was present, likewise improved. Patients who were agitated became quiet; those who were retarded could move with greater ease. There was a diminution of anxiety and tension. Even the self-debasing and derogatory thoughts, the hopeless feelings and suicidal impulses, which could be expressed more easily, were no longer overwhelming and even, on occasion, subsided completely. In general, there was then a striking change in the patient; he became friendly, had feelings of well-being, desired to communicate, had greater ease of motor function and was relaxed without anxiety or tension. This fairly typical reaction made it possible for a clinical evaluation of the structure and depth of the illness. All patients, however, did not have the same order of response; there was considerable individual variability. About 90 per cent of them, if they had not received heavy sedation, showed considerable improvement; the remainder failed to respond.[3]

Benzedrine sulfate likewise is an effective anti-depressant.[4,5,6] In normal subjects and in many fatigue states due to various causes there developed an increased feeling of alertness, a sense of well-being, and an increase in energy with an overcoming of fatigue. Mild euphoria on occasion developed. In our experience, this drug administered either orally or intravenously in patients with depression usually had but mild effects upon their mood. This is consistent with that reported by others.[7,8,9]

When the two drugs were given in combination, a synergistic effect occurred.[10,11] One such advantage of this combination was the analeptic effect of the benzedrine. By its addition the hypnotic effect of the sodium amytal was reduced; that is, drowsiness was diminished and the clinical response to amytal became more apparent. A second advantage was the increase in the duration of the clinical response produced by sodium amytal from an average of 2½ hours with amytal alone to 5½ hours with the combination. It should be noted that the better clinical response was obtained when the benzedrine was administered either with or immediately following the amytal. In addition, when the medication was repeated daily, patients with depression were able to respond with approximately a similar reaction each day both

*This is the fifth paper in a series of psychopharmacologic studies of schizophrenia and depression.
From the Psychopathic Hospital and the State University of Iowa College of Medicine.

in the degree of clinical improvement and in the duration.[12]

These observations suggested that the addition of benzedrine sulfate to the sodium amytal may have an area of clinical usefulness for patients with depression, that of producing symptomatic relief.

The drugs were first used by us for this purpose in 1942. At first they were administered intravenously, day by day, in the mornings. Soon it became evident that the medication could be prescribed orally; then the response developed more slowly and was slightly less pronounced. Also, less medication could be tolerated comfortably. The present technique of administration by mouth is to prescribe sodium amytal mg. 130 to 190 (gr. ii to iii) and benzedrine sulfate mg. 10. The exact dosage is dependent upon the appearance of toxic symptoms, as there is considerable individual variation. The maximum amounts are given. If the patient becomes too drowsy, the amount of amytal is diminished; if too tense, restless, irritable or complaining of palpitation, the benzedrine is diminished. This medication should be administered early in the morning, shortly after arising. If the duration of the response is short, the drugs may be repeated at noon; and on rare occasions at or about 4 p.m. If given later, the benedrine may prevent sleep. No further sedation should be prescribed for insomnia, as sleep usually improves and greater amounts of barbiturate gradually diminish the desired reaction. This regime may be continued daily for a period of a month; longer periods on medication are warranted only in individual cases, as the effectiveness of the medication may gradually diminish. In fact an occasional patient will have a diminution of the response to the drugs within the month. Not all patients will respond to the medication; about 10 per cent fail. In addition, those who have been on barbiturate sedation for some time usually respond poorly. The drugs should be discontinued after a few days' trial if no beneficial response has been noted. Since depressed patients are potentially suicidal, it is usually wise to limit the prescription if the patient is to administer the medication himself; otherwise some member of the family should be responsible for the administration.

Since temporary relief is experienced by this medication, many patients benefit considerably. For purposes of discussion, the group of depressed patients will be considered as two groups, the mild and the moderate or severe. For those patients whose illnesses are mild, one is reluctant to advise hospitalization or electric convulsive therapy. The medication frequently made it possible for them to continue their tasks while receiving psychotherapy as ambulatory patients until their depression subsided. Psychotherapy became a much more applicable tool. With relief from the symptoms, a positive interpersonal relationship was quickly established, which greatly supported the patient. The response to the drugs was helpful then in initiating psychotherapy. This initial period was of considerable importance for it facilitated the establishing of a relationship between physician and patient which continued, in those instances when psychotherapy was complicated and prolonged, beyond the duration of the effectiveness of the drugs. For some patients, a kind, authoritative attitude on the part of the physician, who gave support by means of reassurance and explanations, was sufficient. Other patients required more complex treatment. The sources of conflicts, whether superficial or deep, situational or internalized, needed to be found. Appropriate attitudes were then gradually developed which relieved the sources of the emotional distress, so that the patient could readjust to the life situation in which he had to function.

This combination of drugs was particularly useful to help relieve many of the patients who had frequent but short depressive swings of mood, thus making it possible for them to continue to meet their daily responsibilities. Similarly those patients who used alcohol to obtain relief from depressive mood swings did not need to be dependent on that drug. If they began sodium amytal and benzedrine sulfate when the prodromata of their depressive attacks were recognized, it was possible for many of them to remain relatively symptom-free during the remainder of the period of depression.

The second group of patients, those with moderate or severe depressions, likewise experienced varying degrees of improvement

in their symptoms from these drugs. The medication had its greatest use during the period of their awaiting admission to a hospital. Not only were the patients more comfortable but their care in the home was eased. Incidental to the amelioration of the symptoms of many of the group was the fact that some of these patients recovered. A follow-up study of a group of 60 such patients who ordinarily would have been admitted to hospital showed 14 (23 per cent) in remission. It was not possible to predict which of the severally depressed patients would have the best therapeutic response. It did appear probable that those who improved, had the medication instituted near the termination of their current attack. This is consistent with the fact that depressive illnesses are usually limited in duration. The drugs, therefore, appear to ease the discomfort of the moderate to severe illness primarily, rather than have any effect per se upon the course of the disease.

The administration of the drugs, sodium amytal and benzedrine sulfate, in combination had an ameliorating symptomatic effect upon the majority of patients with primary depression. The degree of response varied considerably from patient to patient. Approximately 10 per cent of the group of patients failed to experience any symptomatic relief whatsoever. In addition, those patients who had been receiving large amounts of barbiturates for their insomnia, likewise, had poor drug responses. It appeared probable that tolerance developed with barbiturate intake to the anti-depressant effects of the drugs. The remainder of the patients had varying degrees of response: the majority had moderate symptomatic improvement, the minority were greatly improved. The drug combination, therefore, has definite limitation in its application.

Summary

1) The ameliorating clinical response of patients with primary depression to intravenous sodium amytal was improved by the addition of benzedrine sulfate; drowsiness was diminished, the duration was increased, and tolerance developed slowly.

2) The medication, administered daily either intravenously or orally, was an aid in the symptomatic therapy of the patient with depression. The discomfort of the moderate or severe illness was modified while the patient awaited hospitalization. A small percentage of such patients while receiving medication recovered (23 per cent). Many mildly depressed patients remained ambulatory rather than hospitalized and were treated by psychotherapy rather than by the more drastic procedure of electric convulsive therapy.

REFERENCES

1 Lindemann, E.: "The Psychopathological Effect of Sodium Amytal," *Proc. Soc. Exper. Biol. & Med.*, 28:864, 1931.
2 Lindemann, E.: "Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal," *Am. J. Psychiat.*, 11:1083, 1932.
3 Gottlieb, J. S.: Unpublished data.
4 Myerson, A.: "Effect of Benzedrine Sulfate on Mood and Fatigue in Normal and in Neurotic Persons," *Arch. Neurol. & Psychiat.*, 36:816, 1936.
5 Nathanson, M. H.: "New Adrenalin-Like Compounds: Their Action and Therapeutic Application," *Calif. & West. Med.*, 57:301, 1942.
6 Reifenstein, E. C. Jr. and Davidoff, E.: "The Psychological Effects of Benzedrine Sulfate," *Am. J. Psychol.*, 52:56, 1939.
7 Dub, L. A. and Lurie, L. A.: "Use of Benzedrine in the Depressed Phase of the Psychotic State," *Ohio State M. J.*, 35:39, 1939.
8 Myerson, A.: "The Sleeping and Waking Mechanisms: A Theory of the Depressions and Their Treatment," *J. Nerv. & Ment. Dis.*, 105:598, 1947.
9 Watts, C. A. H.: "Endogenous Depression in General Practice," *Brit. M. J.*, 1:11, 1947.
10 Gottlieb, J. S. and Coburn, F. E.: "Psychopharmacologic Study of Schizophrenia and Depressions: Intravenous Administration of Sodium Amytal and Amphetamine Sulfate Separately and in Various Combinations," *Arch. Neurol. & Psychiat.*, 51:260, 1944.
11 Myerson, A.: "The Reciprocal Pharmacological Effects of Amphetamine (Benzedrine) Sulfate and the Barbiturates," *New England J. Med.*, 221: 561, 1939.
12 Gottlieb, J. S., Krouse, H. and Freidinger, A. W.: "Psychopharmacologic Study of Schizophrenia and Depressions: Comparison of Tolerance to Sodium Amytal and Amphetamine Sulfate," *Arch. Neurol. & Psychiat.*, 54:372, 1945.

The Dynamics of Juvenile Delinquency*

LUDOLF N. BOLLMEIER, M.D.
Hot Springs, Arkansas

It is a well recognized fact that the child who has spent his entire youth in an institution or foster home, presents a type of his own, and differs in various respects from children who develop under the conditions of family life. These first two years have advantages in all those spheres of life which are independent of the emotional side of the child's nature; he is at a disadvantage wherever the emotional tie to the mother or to the family is the mainspring of development.

The time to begin prevention is earliest childhood. The factors in infant and child care that contribute to health and happiness are feeding, excreting, sleeping and playing; in the manner in which the child is bathed, dressed, loved, welcomed, rewarded and punished, taught and reared. If we want wholesome, normal attitude in our children, not simply toward the eating process, digestion and excretion, but toward all habits and relationships, our babies must be in charge of someone whose attitude toward all physiological processes is one of naturalness and decency. Patience and quiet training by a mother for regularity of bowel movement makes for regularity of disposition; impatience makes for stubborness, constipation, stinginess, and misdirected insistence upon perfection of detail. If a child is allowed to develop symetrically, his sexual tendencies will not remain fixed on his oral or his anal activities.

Behavior patterns and behavior problems, cannot be explained in terms of simple cause and effect relationship, but in terms of motivations. It is not solely the single factor of a broken home which may by itself have a destructive effect on the child. It is the effect of the broken home on the whole mass of factors which develop and create the personality of a child and his adjustment to life. By motivations are meant the responses to the individual's conscious and unconscious emotional needs which are a part and parcel of the entire pattern of adjustment to life. This adjustment is a process which begins in earliest infancy and has its most important period in construction in the early years of childhood. We do not exclude the fact that certain changes in behavior are caused by such specific causes as organic changes in the brain due to injury, inflamation or poisoning.

The infant carries into life the same instinctual drives and urges that we find in the adult. The eventual aim of the care and education of the child is to modify the expressions of the drives and urges, to mold them into a mature, adult, socially acceptable form. The child needs emotional security in order to face the new adjustments it constantly has to make. To give up infantile behavior for behavior on a more adult level means relinquishing an activity from which the child derives immediate gratification, for an activity which at the moment involves self-denial. Example: The child's learning to give up wetting itself when tension arises in the bladder and waiting to urinate until it has reached the toilet. The child is willing to go through this educational process if it receives love in return. If the love is consistant, given as the child needs it, and not given merely to satisfy the inner needs of the adult, emotional security is established because instinctual drives and urges in the infant are always directed towards the parents or those who take care of him.

Juvenile delinquency is a particularly important problem at the moment. The disruption of the normal home structure and influences often occasioned by the need (and exigencies) of war conditions, the absence of older brothers and older sisters and father from the home, mothers going to work, crowded quarters and a host of other factors undoubtedly aggravate a problem which, however, demands equally serious consideration in peace times. The problem can be viewed from two angles. Society's point of view, observed through the eyes of the law; the other, a clinical view, based on the structure and personality of the individual. Many

*Read at meeting of Southern Psychiatric Association, Dallas, Texas, December 6, 1948.

causes have been found to contribute to juvenile delinquency, such as the broken home, loss of a parent, poor economic conditions, bad neighborhood, bad home influence, lack of religious training, inadequate school program, lack of proper recreational facilities, social turbulence, mental deficiency, mental disease and others. There is no doubt that these so-called causes play an integral part in the adjustment of the individual. But the potent role is essentially in the effect that they have no emotional forces in the individuals.

It may be observed that not all children subject to these influences become juvenile delinquents; in fact, the majority do not. These causes cannot be looked upon as entities, but as very complex factors. Statistics indicate that the majority of juvenile delinquents come from "across the tracks" in the poorer neighborhood, conversely, however, the majority of the children from "across the tracks" do not become juvenile delinquents. Psychoanalysis has answered the question "Why siblings of the juvenile delinquents do not become similarly affected." It is due to the subtleties and varieties of the different ways in which each individual reacts to the mass of environmental influences. In the same family, one child obtains love and security, so that it can give up infantile attitudes for adult ones, while another will feel rejected and denied and will therefore retain the infantile attitudes since it cannot progress forward. Essentially, the problem of juvenile delinquency is to be laid at the doorstep of society; for each society can be said to create its own criminals.

Psychoanalysis can treat only a limited number of individuals, but it can spread its knowledge and influence so as to effect a good measure of preventive work. Corrective schools, if adequately subsidized, can operate in a therapeutic manner with all the personnel playing a therapeutic role. But emotional security, which is the bulwark against maladjustment comes from many sources. The socio-economic factors can be looked upon as providing security or not providing security, in a much broader sense than simply that of dollars and cents. If we look upon these socio-economic factors as effecting the emotional and instinctive life of the individual, we see that their importance cannot be minimized. On the contrary, they are of paramount importance.

Experience has taught that the period from birth to the age of five or six, is the reservoir from which one's character emerges. The reaction of the child in that early period will determine the mode of his reactions in all experiences in later life. The different instincts and the strength of the impulses connected with oral, anal, and genital phases of development, strongly influence and are directly connected with the character attributes which manifest themselves in later life. Character difficulties are always a result of poor adjustment in early childhood. Most often they are a direct consequence of the inability to solve the love and hate relationships to parents during the O Edipus period. The healthy solution of the O Edipus complex will bring about the identification processes in the child.

From whatever angle we look upon character formation, we are unable to understand it, unless we try to understand and appreciate the O Edipus conflict and also the relationship between the total personality, the "Id," the "Ego," and the "Super-Ego." To childhood, these three components of the total personality are not yet solidified, thus wishes and desires appear in a primitive form. To transform them into a more acceptable outward form, the young child must learn to adjust himself. In the slow process of becoming "sociable," his strivings will metamorphose into a more acceptable expression. If we realize how weak the child's ego is during the course of that early development, and how necessary it is for him to depend on parents and teachers, as it is they who help form his super-ego and who are responsible for his actions in later life, then we can more fully appreciate the parent's and teacher's role in character formation, we can then have an idea of the amount of love, patience and understanding which a healthy upbringing requires.

To be able to produce some change in the child in the various periods of its developmental stages, the parents and those under whose care the child is placed, must make sacrifices and occasionally adjust themselves to the child's demands. The tendency to become the exact opposite of ones parents, can become the dominant factor as a result of

an unhappy environment. Thus we find the drunkard's son becoming a priest, and the teetotaler's child a drunkard. The character of a person is the sum of his instinctive reactions to social environment.

There are no problem children, only problem parents. The teachers are the second line of defense in the child's development, as they begin where the parents leave off. Parents and teachers must permit children to express their anger, instead of forcing them to repress it, lest they lose their love and affection. The fear of the loss of love from those who are over them, is the greatest threat to the child's security.

Summary

Children that develop under the conditions of family life, have many advantages over those children that live in institutions and foster homes. The first six years of life are the most important, and well adjusted parents is the *sine quo non* to well adjusted children. There is no substitute. All behavior must be explained in terms of motivations. Juvenile delinquency has two angles; law and clinical. Many causes are pointed out. Neighborhoods, bad homes, school, death of parents, etc. We must remember that it is not the environment, but the child's reaction to the environment. It is society's problem and society should assume responsibility and treat the problem.

Combined Penicillin and Malarial Fever Treatment in Cerebrovascular Syphilis

(REPORT OF A CASE AND REVIEW OF LITERATURE)*

WALLIS L. CRADDOCK, M.A., M.D.
Fort Logan, Colorado

The proper evaluation of success in treatment of neurosyphilis has always been a problem since Wagner-Jauregg[1] reported the beneficial effect of malaria in the treatment of dementia paralytica over a quarter of a century ago. As early as 1924, the observation was made that proper evaluation of the spinal fluid syndrome, with special emphasis on the cell count, enabled one to forecast with considerable accuracy the degree of activity of the syphilitic infection in the central nervous system. The efficacy of treatment evaluated on clinical improvement alone has proven to be a serious mistake. A proper evaluation of the spinal fluid findings requires (a) a cell count, (b) determination of the total protein content, (c) a specific test for syphilis and (d) a colloidal gold test.

A cell count of more than 4 cells per cc. is evidence of an active process; the cell count affords the most valuable information as to the activity of the syphilitic infection in the central nervous system. It has been found that after successful fever therapy the first of the abnormalities of the spinal fluid to be corrected is the abnormal cell count.

The spinal fluid protein values, the readings in the colloidal gold test and the titers in the quantitative Wasserman test decrease gradually, usually in the order given, according to Lange and Harris.[2]

It is manifestly impossible to review the massive data of therapy in neurosyphilis in a short paper. However, articles dealing with combined penicillin and malarial fever therapy have not been numerous. Gammon and Stokes[3] showed their enthusiasm in one of the earliest reports in 1946: "Malaria in paresis is superior to penicillin alone in the clinical improvement produced when compared with the first year or two of penicillin responses; but penicillin rapidly overtakes malaria in the second and equals it in the third year of observation. It begins to look as if penicillin alone were the equal of malaria in paresis. Whether the combination or sequence of the two can improve on either alone, remains to be seen . . . in tabo-paresis

*From the Medical Service, Veterans Administration Hospital, Fort Logan, Colorado.

the fluid improvement under penicillin definitely surpasses that obtained with malaria and the symptomatic improvement with penicillin is equal after the second year; in meningovascular neurosyphilis results are markedly superior serologically and equal clinically." Their patients were treated with the "low dosage" schedule of 4.8 million units and some were given "high dosage" schedules of 4.8 to 10 million units of penicillin. These dosages will be referred to in the course of this paper.

Moore and Mohr[4] claimed that "in the more serious parenchymatous forms (paresis, tabes dorsalis, primary optic atrophy, nerve deafness) the combination of penicillin and fever from induced malaria simultaneously administered may be superior, both from clinical and laboratory standpoints, to penicillin alone." However, Rose and Soloman[5] point out that the advisability of prescribing malarial fever therapy is not held by all writers. It is surprising that Koteen and Doty[6] had so much confidence in penicillin. These authors state that penicillin alone, as the sole anti-syphilitic therapy for patients with meningovascular syphilis and paresis, is justified. Their patients received 4 million units in 5 days.

Most authors reporting treatment with penicillin therapy have given between 3 and 6 million units. There is surprisingly little data in the literature on the subject of the optimum total dose of penicillin in late symptomatic neurosyphilis. Epstein[7] points out the difficulty of presenting therapeutic results in neurosyphilis. In general, he follows a program of giving a "low dosage" schedule of penicillin and favors a total of 50 hours of malarial therapy, in addition. Brunsting[8] believes a course of penicillin treatment is useful as an introductory phase of therapy for patients who have a pronounced degree of meningovascular syphilis or who are in an agitated stage of paresis. He believes that penicillin will reduce the fulminating process so that fever treatment can be given with less risk of upsetting the balance.

Dattner[9] concluded that in his experience penicillin had proved to be surprisingly effective in cases of neurosyphilis. Not only did it prove to be as effective as malaria, but it displayed the great advantage of being much less toxic. He was of the opinion that penicillin might ultimately replace fever therapy. Reynolds, Mohr and Moore[10] believe that the use of penicillin and malaria is productive of significantly better results than the use of penicillin alone. The effectiveness of concurrent penicillin-malarial therapy is such as to make it, in their opinion, the treatment of choice for patients with dementia paralytica. This opinion is likewise shared by O'Leary[11] who states that treatment with penicillin alone has never given a clearcut clinical remission in a patient with frank dementia paralytica. He feels that the partial remissions that sometime occur are not only incomplete, but are of short duration. "However, penicillin plus fever therapy produces complete remissions. The results are erratic following use of penicillin in treatment of meningovascular neurosyphilis." Heyman[12] also favors combined penicillin and fever therapy instead of penicillin therapy alone in neurosyphilis.

It is apparent that a large percentage of the reported cases treated by combinations of penicillin and malarial fever therapy are considered to be asymptomatic neurosyphilis. There is sufficient evidence at hand to justify the treatment of asymptomatic neurosyphilis with at least one course, or possibly several courses of penicillin, before resorting to fever therapy. Further investigation and study are needed to establish the permanence of improvement as judged by spinal fluid findings and the absence of clinical relapses following therapy with penicillin alone in neurosyphilis. As Rose and Soloman have re-emphasized, "No one seems to know the modus operandi of malarial therapy, yet no one seems to want to cast it aside because of this inadequate understanding or because of its dangers."

Case Report

The patient, a 52 year old male, was admitted to the Veterans Administration Hospital, Fort Logan, Colorado, on January 17, 1947. He was unable to walk because of apparent weakness of the left side of the body. He was completely disoriented and displayed slurring, incoherent speech. He was incontinent of urine and feces. His mouth was drawn to the right. The deep reflexes were hyperactive, and the superficial reflexes were absent on the left. There was no muscle atrophy. The pupils were unequal, with con-

traction of the left pupil. Both pupils reacted sluggishly to light. The eyegrounds were normal. Blood pressure was 120/82; pulse, 80, full and regular; temperature, 99 degrees F. (R.). No abnormalities of the heart and lungs could be demonstrated.

History: In 1943, it was learned that the patient had syphilis. The treatment with arm and hip injections was begun at once and was continued for three years. He remained asymptomatic during this period. However, in September, 1946, it was noticed that he exhibited evidence of central nervous system involvement as indicated by slurring, rambling, and dysarthric speech. The blood serology was found to be strongly positive for syphilis. A spinal fluid examination had unfortunately not been done at that time. The physical examination was said to have been negative, although there was a slight tremor of the hands and the left pupil was smaller than the right. Both pupils reacted to accommodation, but only sluggishly to light. In September, 1946, he had been given 4 million units of penicillin over a period of 9 days.

On January 6, 1947, the patient was said to have suddenly become ataxic, with definite weakness of the left side of the body. For several months he had been noticeably more irritable and forgetful. Prior to admission to Fort Logan, he was treated symptomatically at home, but when it was found necessary to apply restraint measures he was brought to the hospital.

Laboratory Data: At the time of admission a complete blood count and urinalysis were normal. Blood serology was strongly positive. The spinal fluid pressure was 240 mm. water; the cell count of the spinal fluid was 150 per cc., predominately lymphocytes. The spinal fluid in addition showed a strongly positive Wasserman reaction, a colloidal gold curve of 5555553210, a total protein of 100 mgms. per cent, a sugar content of 64 mgms. per cent and was strongly positive for globulin. During the course of intensive penicillin and malarial therapy, frequent non-protein nitrogen determinations, urinalyses and blood counts were taken. These continued to be normal except for a slight anemia. Following iron therapy and the discontinuance of the malarial therapy, the blood cell count and the hemoglobin returned steadily to normal. Blood serology has remained positive, up to the last examination made on July 12, 1948.

On roentgen-ray examination, the heart and the lungs appeared normal.

Follow-up spinal fluid examinations are summarized as follows:

	3/22/47	7/30/47
Cell Count:	4	2
Protein, Total:	57	60
Globulin, Pandy:	+++	+
Wasserman:	++++	++++
Gold Curve:	5554331100	5543210000
Sugar:	63	65
Pressure:	Normal	Normal

	12/8/47	7/12/48
Cell Count:	4	2
Protein, Total:	52	32
Globulin, Pandy:	Trace	Trace
Wasserman:	Negative	Negative
Gold Curve:	0012210000	0001100000
Pressure:	Normal	Normal

Clinical Course: At the time of admission, this patient showed all signs of an acute downhill course. It was necessary to catheterize him regularly and he remained incontinent of feces. On January 25, 1947, he suddenly developed a severe chill with a very irregular and thready pulse of 140 per minute and a rectal temperature of 105 degrees F. Respirations were labored, very rapid and shallow. There were generalized, athetoid tremors; it was felt that the left facial paresis was much more prominent than it had been. The deep reflexes were absent. Blood pressure was 120/90. He became cyanotic; it appeared that he had developed a cerebrovascular insult. However, three hours after the onset of this episode, he began to respond, without medication, and the ashen-gray color of the mucous membranes had disappeared. Six hours later he appeared not to have suffered from the event.

Penicillin therapy was cautiously instituted on January 26, 1947. A total of 11 million units were given terminating on March 1, 1947. The patient was injected intramuscularly with 6 cc. of vivax malarial blood on February 20, 1947. Strict vigilance was instituted regarding possible cardiac collapse and other complications in a patient recently having had a probable cerebrovascular accident. The first malarial paroxysm occurred on March 4, 1947, and progressed every other day until March 25, 1947, when the therapy

was terminated after eleven chills or 48 hours of fever over 104 degrees F. By that date, the patient was fully oriented and very cooperative. He had been getting physiotherapy since February 1, 1947. This seemed to be of use in restoring strength to his left side. He was fully ambulatory by March 10, 1947, and able to go to the mess hall and to the Department of Occupational Therapy.

A second course of 11 million units of penicillin was given between March 22 and April 15, 1947. On April 2, 1947, a Wechsler-Bellevue intelligence test was obtained which showed rather extensive scattering and illogical thought processes.

The patient was discharged from the hospital on April 17, 1947. He was instructed to return for regular follow-up examinations. He has since been seen on four occasions. It is quite apparent that he had made a very good "social recovery," with no recurrence of tremors, dysarthria, mental confusion or irritability. A repeat Wechsler-Bellevue test on July 12, 1948, showed obvious improvement in his mental condition. He has made a good living for his family as a gardener; physical examination on July 12, 1948, was negative except for the persistently contracted left pupil.

Comment

The case here reported presented the general picture of severe paresis, although the onset was of acute vascular type. We appreciated that the dangers of treatment with malaria after a vascular onset were much greater than in an ordinary uncomplicated paretic syndrome. However, the fact that the disease in this case was progressing with such rapidity and severity made heroic therapy justified. It was felt that large doses of penicillin should first be given cautiously. We must remember that the patient with this type of vascular accident may have another accident whether or not malarial therapy is given. This had been demonstrated with at least two such episodes seen in this case in a very short period.

It is believed that any case of this type requires such intensive combined penicillin and malarial therapy, in view of the rather poor results using smaller doses of penicillin reported in the literature. It is agreed that the full course of malarial therapy is indicated.

Summary

Literature dealing with combined penicillin and malarial therapy in neurosyphilis has been reviewed. A case of neurosyphilis with repeated cerebral vascular accidents treated during the so-called "asymptomatic state" with "adequate" penicillin therapy previous to hospitalization, has been presented. Treatment consisted of intensive penicillin therapy (22 million units) plus "full dose" malarial therapy; the patient has been able to make a complete "social recovery" and his spinal fluid is normal after 18 months.

REFERENCES

1 Wagner-Jauregg, J.: "Fever Therapy, Its Rationale in Diseases of the Nervous System," *Edinburgh Med. Jour.*, 40:1 (July) 1936.
2 Lange, C. and Harris, A. H.: "Interpretation of Findings in the Cerebrospinal Fluid," *Arch. Neur. and Psychiatry*, 53:116 (Feb.) 1945.
3 Gammon, G. D. and Stokes, J. H.: "Penicillin Therapy Alone in Neurosyphilis: Analysis of Clinical Results," *Ann. Int. Med.*, 25:412 (Sept.) 1946.
4 Moore, J. E. and Mohr, C. F.: "Penicillin in Treatment of Neuro-syphilis (Asymptomatic)," *Am. Jour. Syph., Gonorrh. and Ven. Dis.*, 30: 405 (Sept.) 1946.
5 Rose, A. S. and Solomon, H. C.: "Study of 100 Cases of Neurosyphilis Treated with Penicillin," *J.A.M.A.*, 133:5-10 (Jan.) 1947.
6 Koteen, H. and Doty, E. J.: "Penicillin Therapy in Neurosyphilis," *Am. Jour. Syph., Gonorrh. and Ven. Dis.*, 31:1 (Jan.) 1947.
7 Epstein, N. N.: Discussion, *J.A.M.A.*, 133:10 (Jan.) 1947.
8 Brunsting, L. A.: Discussion, *J.A.M.A.*, 133:10 (Jan.) 1947.
9 Dattner, B.: "Value of Penicillin in Treatment of Neurosyphilis," *Arch. Neur. and Psychiat.*, 57:50 (Feb.) 1947.
10 Reynolds, F. W., Mohr, C. F. and Moore, J. E.: "Penicillin in the Treatment of Neurosyphilis," *J.A.M.A.*, 131:1255 (Aug. 17) 1946.
11 O'Leary, P.: Discussion, *J.A.M.A.*, 133:10 (Jan.) 1947.
12 Heyman, A.: "Treatment of Syphilis of CNC with Penicillin," *Am. J. Med. Sc.*, 213:661 (June) 1947.

Neurological Clinical Pathological Conference

OF THE CINCINNATI GENERAL HOSPITAL

CHARLES D. ARING, M.D., Editor

Case No. 226349

Presentation

A 45 year old, colored, housewife arrived at the receiving ward at eight o'clock on the evening of June 7, 1947 complaining of numbness below the waist and inability to move the legs. She enjoyed good health until May 29, 1947 when she experienced an episode of epigastric pain which was relieved by vomiting. She suffered no further distress until June 5 at which time she again experienced upper abdominal pain and vomited, this time without relief. The following morning because of persistent discomfort she visited the clinic of a private hospital. At that time she also complained of a sensation of numbness in her feet for which the examiner apparently could find no explanation and no treatment was administered. She was thought to be suffering from cholecystitis. During the day there was gradual spread of numbness up to the knees and some fever and malaise. Upon awakening on the morning of June 7, she found herself unable to move her legs or to urinate, and she was numb below the waist. She had mild headache and slight fever; her bowels and bladder had not evacuated since June 6.

She had been obese for a long time. Her ovaries were said to have been surgically removed in 1930. Four years ago after a bout of vomiting, she was found to have syphilis for which she received rather prolonged antiluetic therapy. The last injection was in February, 1947, when she received a blood test and cerebrospinal fluid examination and was told that she was cured.

On examination in the receiving ward at 8:00 p.m., the patient was oriented, pleasant and cooperative. Other than slight pain and resistance of the neck to complete flexion, the abnormal physical findings were limited to the lower part of the trunk and the lower extremities. She was quite obese; there was a well-healed suprapubic scar; the bladder was palpable to the level of the umbilicus; the lower extremities were flaccid and completely paralyzed except for slight movement of the toes of the left foot with the exception of the great toe. The deep reflexes were absent in the legs, the abdominal skin and plantar reflexes were not elicitable, the sphincters were relaxed; and there was lack of appreciation of all sensation below the level of the 10th thoracic dermatome.

By midnight she had become so irrational, noisy and restless that it was necessary to restrain her. Her face assumed a grayish pallor, the palpebral fissures widened, and her respirations became labored. Forty-five minutes later she was comatose; her face was ashen, and she was drenched in perspiration. Her respirations were extremely rapid and gasping and became increasingly weak and irregular. Thick, clear mucous poured from the nose and mouth. She ceased to breath at 1:00 a.m. on the morning of June 8. The heart continued to beat with the aid of artificial respiration and intracardiac stimulants for an additional 30 minutes. Her hospital stay had consumed only 5½ hours.

Laboratory Data: At the time of arrival in the receiving ward, the temperature was 103 degrees F, the pulse rate 110, respiratory rate 28, and the blood pressure 130/80. By midnight, the respiratory rate was 40 and forty-five minutes later had risen to 60. There was concomitant elevation of the pulse rate to a terminal high of 140.

The cerebrospinal fluid:

Initial Pressure, mm Water	280
cc. Removed	6
Final Pressure	250
Appearance	Cloudy
WBC/cmm	2800
Polys.	100%
Prot. Mg %	385
Sugar Mg %	70
Culture	No Growth

The cerebrospinal fluid Wassermann was negative.

Differential Diagnosis

Dr. Harry M. Salzer: On admission to the hospital the findings were those of an acute transverse spinal cord lesion at the level of D-10. There was slight pain and resistance

of the neck to complete flexion suggesting meningeal irritation. The patient went into shock quickly, her hospital life lasting but 5½ hours.

The results of blood serological study are not known. The cerebrospinal fluid examination was of assistance; the initial pressure was high—280 mm., the final pressure was high also—250 mm. The increase in pressure may have been the result of an infectious process, although respiratory distress must be considered in its genesis. The cell count indicated that there must have been an acute process in the meninges. The sugar content of 70 mg. makes one think that the process was not an acute infectious one. The total protein of 385 mg., makes one suspect a block although no information concerning such was available; the pressure of 250 mm. after the removal of 6 cc. of fluid makes one think there was no block.

In making a differential diagnosis, tumor is considered unlikely because of the fever, signs of infection in the cerebrospinal fluid, and the rapid onset. In the absence of any history of it, trauma may be ruled out.

In appraising a vascular lesion, aortic aneurysm producing erosion of a vertebra and causing failure of circulation to the spinal cord would be unlikely; the cerebrospinal fluid cell count is against it. Dissecting aneurysm would be unlikely because of the lack of pain and because of the nature of the onset. With dissecting aneurysm the heart would most likely fail first, then respiration. The opposite was true in this case. Anterior spinal arterial or venous thrombosis would have come on more abruptly and not over several days. This type of cell count would not have been present; the irrationality is also against this diagnosis.

I believe the answer lies somewhere in the realm of the infection. An abscess from an infected embolus might be ruled out because there was no evidence of associated cardiac involvement.

An epidural abscess would have to be considered. However, there was no skin infection or other known focus. The cerebrospinal fluid pressure of 280 mm. initially is against an epidural abscess. If an epidural abscess had ruptured into the cerebrospinal fluid, the picture could have been something like this although the manner in which death supervened is against it because the respiratory rate suggests a higher lesion. I believe she had some pathological process above D-10 because of the irrationality and restlessness. The mucous pouring from the nose and mouth suggests difficulty in swallowing and therefore a medullary lesion.

Acute syphilitic meningomyelitis is felt to be remote because the patient had been receiving treatment for lues and was pronounced "cured," the cell count was too high, and the cerebrospinal fluid serological study was negative. She might have had a gumma in the cord, but again the mode of dying is against a gumma.

Therefore, it is my opinion that the patient had some type of acute infectious meningomyeloencephalitis. The main reasons for making this diagnosis are the acutely developing cord lesion, high cerebrospinal fluid pressure and cell count, and signs of meningeal irritation, soon followed by signs that the disorder spread upward to the medulla. The abdominal pain and vomiting probably were the result of radicular irritation in the meninges. In considering the nature of an acute infectious meningomyeloencephalitis, there was no growth in the culture so that this could not be determined. It may have been the result of a virus infection.

Dr. Howard Krouse: By your diagnosis, do you mean acute disseminated encephalomyelitis?

Dr. Salzer: I think you can consider it the same. Was there any progress note in the chart which would indicate that the patient was moving her arms? In other words, was the disease ascending?

Dr. Aring: The lumbar puncture was performed at 11:30 p.m. Immediately thereafter she was quite restless and irrational, struggling against the restraints with her arms and perspiring freely. The next note at 12:45 a.m. records shock and coma.

Dr. Daniel Osher: Was there any note about tenderness of the spine?

Dr. Aring: No, up to the time that she became irrational, she was relatively comfortable.

Discussion of Pathology

Dr. I. Mark Scheinker: Examined grossly, the brain showed uncal compression bilaterally and slight cerebellar pressure cone.

On sectioning the brain, there was swelling of the cerebral hemispheres with compression and obliteration of the lateral ventricles. The sectioned spinal cord was swollen and soft, almost fluctuant, especially in the mid-thoracic region, where it was difficult to differentiate between gray and white matter.

It is difficult to show you the changes because of the amazing destruction of the parenchyma of the mid-thoracic spinal cord. Instead of gray and white matter we find necrosis and polymorphonuclear leucocytes. A few gitter cells were found in the area of complete destruction of parenchyma. The perivascular spaces were packed with polymorphonuclear leukocytes. The leptomeninges were slightly infiltrated, involvement secondary to that of the parenchyma. In addition, we see a vascular reaction that I have never seen before; the entire blood vessel wall in a state of coagulation—they are thickened and homogenous. There was nothing abnormal about the epidural or subdural spaces. Sections from the cervical and sacral regions of the spinal cord showed a minimal degree of the same process found in the other segments. Sections from the brain stem were normal except for an occasional cuffing of some of the smaller blood vessels with hematogenous cells. The viscera showed no signs of infection.

Dr. Osher: Were the roots involved?

Dr. Scheinker: No they were normal. The medullary picture confirms the acumen of Dr. Salzer, who suspected a lesion higher than the thoracic region. There were several perivascular lesions in the medulla in which leucocytes and a few gitter cells were found.

The neuropathological diagnosis is purulent myelitis of undetermined origin, with minimal involvement of the medulla. The etiology is not clear to say the least. I could find nothing in my reading about this type of myelitis, a form that I have never met before.

There is little difficulty in differentiating this condition from acute disseminated encephalomyelitis which was considered in this conference a few months ago when Doctor Aring discussed the case. We base the diagnosis on the type of cell predominate in the disease; in the latter we find lymphocytes, whereas in the case discussed today we have little besides polymorphonuclear leucocytes.

Clinical Diagnosis

Purulent meningoencephalitis.

Dr. Salzer's Diagnosis

Acute infectious meningoencephalitis.

Anatomical Diagnosis

Purulent myelitis and medullary involvement of undetermined origin.

Cerebral edema.

Acute congestion and edema of lungs.

Markedly acute congestion and toxic changes of the viscera.

Chronic focal suprarenalitis.

Moderate interstitial fibrosis of the pancreas.

Dr. Osher: You found no organisms in your sections; it seems to me that this disease does not have to be an infection.

Dr. Scheinker: The presence of so many polymorphonuclear leucocytes in the spinal cord makes it seem relatively certain that we are dealing with infection.

Dr. Osher: Acute infarction of the nervous system may result in polymorphonuclear leucocytic reaction early, and there may be an intense cellular reaction in Devic's disease which is without organisms, of course.

Dr. Aring: I am reminded that in poliomyelitis, the initial cellular response is polymorphonuclear leucocytic, replaced later by microglial reaction. I wondered if this was not an analogous situation. We have felt that if it would be possible to tap cases of poliomyelitis in the first stage of the disease, we would find polymorphonuclear leucocytes in the cerebrospinal fluid. Returning to the case discussed today, when organisms cannot be grown in a culture of such a cerebrospinal fluid as this it would appear to be good evidence that we are not dealing with a pyogenic infection.

Dr. Krouse: There is so much abnormal in this cerebrospinal fluid that it seems the sugar should also have been abnormal if this were a pyogenic infection.

Dr. Aring: This case leaves me with the feeling I have frequently when dealing with acute or even chronic cord lesions. The spinal cord isn't very large, and its reactions are limited; spinal cord syndrome sometimes do not differ markedly in their clinical manifestations. I find the differential diagnosis of diseases of the spinal cord among the most

difficult in neurology, and well it might be since we note what trouble the pathologist is having convincing us about differential diagnosis in this case with the spinal cord before our eyes.

We have had no explanation for the edema of such vital organs as the brain and lungs which perhaps was associated with the clinical state of shock and the rapid death. I find myself relatively baffled by the case, the presentation of which leaves something to be desired.

Editor's Note: These conferences are conducted under the direction of Charles D. Aring, M.D., Professor of Neurology, assisted by I. Mark Scheinker, M.D., Assistant Professor of Neuropathology, and Howard Krouse, Assistant in Neurology, University of Cincinnati College of Medicine.

Book Reviews

Personality Projection: In The Drawing of the Human Figure. By Karen Machover, Ph.D. Springfield, Illinois: *Charles C. Thomas,* 1949, pp. 179.

In this monograph, the author presents a pioneer work in the use of the Drawing of a Human figure in aiding the clinical interpretation of specific psychiatric cases. This work grew out of the administration of Goodenough's Drawing-of-a-Man test for usual I.Q. purposes. It was discovered that careful study of the individual drawings often yielded rich clinical material not related to the intellectual level of the subject. Later this device was extended to adults of all ages. This monograph discusses briefly the development of this projective technique and details the method of administration used by the author. In some detail the principles of interpretation used by the author are elaborated for the various parts of the body, the clothing, structural and formal aspects and the conflict indicators. Seven illustrative case studies including normal children, normal adults, neurotics, and psychotics are presented in detail with brief clinical histories, drawings and interpretations.

The author expressly states that the present monograph is not intended as a check-list of "signs" to be used mechanically. Instead stress is laid primarily upon interrelated patterns of drawing traits as they may reflect the dynamics of symptom organization in a particular diagnostic category. These patterns were checked by Rorschach and handwriting experts and the author feels that in the future this method may assume an important role in the evaluation of psychiatric syndromes. The economy, ease of administration, communicability of the method as well as the apparently reliable data obtained tend to substantiate this feeling.

This little book is generally a well presented introductory work on a new but clinically important projection technique.

—John K. Torrens, M.D., Galveston, Texas.

The Case of Augustus D'Este: By Douglas Firth, M.D. Publisher: *Cambridge, at the University Press, New York, MacMillan Company,* 1948.

In December 1822, Augustus D'Este, the illegitimate son of the Duke of Sussex, sixth son of George III, wrote in his journal, "....my eyes were so attacked that when fixed upon minute objects indistinctness of vision was the consequence . . Soon after, I went to Ireland, and without anything having been done to my eyes, they completely recovered their strength of distinctness of vision."

Over the period of the next twenty-six years, the journal is filled with mention of other symptoms of the disease of which the above was the first sign. Weakness and numbness of the extremities soon developed along with a loss of sphincter control and spasm of the leg muscles. Occasional short periods of remission did occur which sometimes coincided with a change in treatment and were attributed to such. The over all picture, however, is one of a gradual increase in severity of the symptoms with D'Estes last years being made particularly miserable by vertigo, weakness, spasm and pain which confined him to a "chair on wheels." The various treatments used varying from douches to electrical stimulation are recorded in great detail, particularly the prescriptions. Although the symptoms of nystagmus and scanning speech are not mentioned and the immediate cause of death is unknown, the clinical picture of multiple sclerosis as presented here is otherwise remarkably complete. This disease was not adequately described by medical men, however, until twenty years after D'Este's death.

The journal of Augustus D'Este was discovered in England in 1940 during the drive for waste paper and was presented to the Royal College of Physicians, London. Dr. Douglas Firth, who has since died, edited this manuscript and presents it in full, preceded by extracts from other papers and followed by brief notes from D'Este's last diary. The other extracts serve to show something of the background and type of personality of Augustus D'Este and to record the psychological traumata which may be of interest in the etiology of multiple sclerosis.

As an intern of medical history this little book is extremely interesting. In particular, the picturesqueness with which the familiar symptoms of multiple sclerosis are described makes this fasconating reading.

—John Torrens, M.D., Galveston, Texas.

Sedation and Euphoria for Nervous, Irritable Patients

VALERIANETS-DISPERT®

Each tablet contains Ext. of Valerian 0.05 gm. dispergentized for maximum efficiency. Odorless and tasteless. Non-habituating. ACTION AND USES: A mild central nervous system depressent. For use in emotional upsets, anxiety states, nervous insomnia, the nervous syndrome of the menopause and of arteriosclerotic subjects.

1 or 2 tablets as required or 3 on retiring. Bottles of 50, 100 & 500.

STANDARD PHARMACEUTICAL CO., INC. 1123 Broadway, New York